The importance of team work

Fuchs, B

Cancer Research in Switzerland

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Eva-Fiore Kovacovsky (*1980) Born in Bern, lives and works in Amsterdam and Berlin.

Eva-Fiore Kovacovsky examines phenomena in the world of plants, which she collects according to her own criteria and uses as a starting point in her artworks. Kovacovsky works with several different reproduction techniques and methods of photography. She abstracts, manipulates, arranges, and reproduces parts of plants and in this way generates artworks that deal with our own perception.

For her *Fotogramme* series shown here, Kovacovsky works with leaves that she has collected because of their distinctive patterns of perforations. She uses the leaves with holes eaten into them by beetles and caterpillars as negatives, places them in the negative carrier of a colour photographic enlarger, and exposes them on photographic paper. She constructs intuitive images by working in a playful way with different enlarging lenses, image details, multiple exposures, shifting of the filters in the colour mixing head, and photographic paper.

www.kovacovsky.com

Eva-Fiore Kovacovsky's work is in public and private collections. She is represented by the STAMPA gallery in Basel (www.stampa-galerie.ch).
All images courtesy of Eva-Fiore Kovacovsky and STAMPA, Basel

At the request of the artist, the original titles of her works have not been translated.

Cancer Research in Switzerland

Table of contents

Editorial

Thanks to donations of more than 20 million francs, in 2013 the Swiss Cancer Research foundation, the Swiss Cancer League, and the cantonal and regional cancer leagues invested another new record sum in cancer research. This is a wonderful result not only in quantitative terms; the funding of research and also the funded research projects achieved satisfying results also in terms of quality.

Research funding by the Swiss Cancer Research foundation and the Swiss Cancer League was assessed comprehensively in 2013 by means of an independent external evaluation. As a part of the evaluation, more than 400 publications produced by funded research projects from 1998 to 2006 were rated. The results showed that the researchers especially in basic biomedical, translational, and epidemiological research published many high-quality and important papers that achieved top ratings in a comparison with nine European funding institutions.

The results of a survey of the researchers were also positive: The majority of the researchers rated the commitment of the two funding institutions to their own research activities as high to very high and to cancer research in Switzerland in general as positive to very positive. Nearly nine of ten survey respondents stated that the grant application process from submission to review was transparent, fair, and of high-quality. And also a comprehensive analysis by a group of six independent, internationally renowned experts gave excellent marks for central aspects such as research promotion, quality assurance, monitoring, structures, and resources.

The experts were particularly impressed by the quality of the work of the Scientific Committee, the group of 17 experts who review approximately 170 to 180 applications for grants and bursaries each year according to defined criteria and international standards.

Thomas Cerny

Jakob R. Passweg

They thus perform an extremely valuable service for the Swiss Cancer Research foundation and the Swiss Cancer League. Thanks to the work of the Scientific Committee, only the highest quality and most promising research projects are funded. We therefore extend sincere thanks to all members of the Scientific Committee and especially to Prof. Martin F. Fey, MD, who has served as president of the Scientific Committee since 2006 and will be stepping down at the end of this year. Prof. Nancy Hynes, PhD, molecular biologist and breast cancer specialist, has been elected the new president and will take office at the start of 2015.

We would like to express our heartfelt thanks to all charitable donors for your support. Your generosity and loyalty make it possible for us to fund outstanding cancer research aiming to continue to improve chances of survival and quality of life of patients with cancer.

Prof. Thomas Cerny, MD
President of the Swiss Cancer Research foundation

Prof. Jakob R. Passweg, MD
President of the Swiss Cancer League

Funding internationally top-level cancer research

In 2013 the Swiss Cancer Research foundation (SCR), the Swiss Cancer League (SCL), and eight cantonal cancer leagues (CCL) gave a total of 20.4 million francs to cancer research in Switzerland – which was again a new record sum. Also gratifying are the results of an independent external evaluation that gave the work of the SCR and the SCL in research funding and also the quality of the funded projects excellent marks. We thank all of the charitable donors for their trust and support.

Each year, the SCR, SCL, and several CCL grant about 20 million francs to universities, hospitals, and academic research institutions for oncological research. The SCR, which contributes approximately two-thirds of this sum, is dedicated exclusively to supporting cancer research. About one-third of the funds are contributed by the SCL and several CCL. The SCL and the CCL are engaged at a broad level in the fight against cancer; in addition to funding cancer research, their priority tasks also comprise supporting and advising persons with cancer and their families, cancer prevention, and early detection of cancer.

Contrasting developments

In Switzerland and in most European countries, two basic tendencies have characterized cancer developments in the last 20 years: Cancer incidence is increasing, but death rates are declining. The fact that there are more and more new cancer cases each year is primarily the result of demographic developments, since cancer is more frequent with increasing age. The main reasons for the welcome decline in cancer mortality are especially improved early detection and great advances in diagnosis and treatment. Today, more than half of persons with cancer – approximately 37,000 new cancer cases are diagnosed each year – can be treated successfully.

Nevertheless, each year approximately 16,000 patients die of cancer, and with some types of cancer, such as pancreatic cancer or brain tumours, the chances of successful treatment are low. Further advances in the fight against cancer are therefore urgently needed – not only to improve survival rates and the quality of life of persons with cancer but also to be able to detect cancer as early as possible and to prevent cancer. And to achieve this, we continue to need great efforts in research.

Diverse research areas

The SCR, SCL, and the CCL support research projects across the entire broad range of cancer research, grouped in four central research areas: basic, clinical, psychosocial, and epidemiological cancer research. *Basic biomedical research* studies biological processes, how cancer cells develop, proliferate, and spread in the body. *Clinical, laboratory-oriented research* – also called translational research – works with cancer cells and tumour tissue to identify new biomarkers or targets, so that better diagnostic methods or more effective drugs can be developed. In *clinical, patient-oriented research*, clinical trials are conducted with patients with the aim to optimize existing treatments or to establish new, improved treatments.

Rolf Marti, PhD
Head of the Scientific Office, Swiss Cancer League and director of the Swiss Cancer Research foundation

Psychosocial research studies the psychological and social effects of cancer with the aim to improve the quality of life of persons with cancer and their families. *Epidemiological research* examines, for example, the rates of cancers in the population and the factors that have an effect on cancer risk, such as age, gender, smoking habits, amount of physical activity, nutrition, social environment, and environmental factors. Also funded are research projects in nursing sciences, prevention, public health, and health services research, which analyses how effective, expedient or economical medical health services are under everyday conditions.

Evaluation confirms quality

In 2013, an extensive external evaluation was conducted to assess the efficiency and success of the research funding by the SCR and the SCL and the quality and significance of the research findings of the research projects funded. The results were very gratifying: The work of the SCR, SCL and especially the Scientific Committee, which peer-reviews the grant applications submitted, was rated very good overall. The SCR and the SCL fund research projects that are of excellent quality and produce many publications of great scientific importance – with top-level values in an international comparison.

For the foundation board of the SCR and the board of the SCL, research quality was not only the top priority in their funding activities in the past: It continues also in the future to be the most important decision criterion in selecting projects for funding. A guarantor of quality assurance is the sound work of the 17 experts on the Scientific Committee, whose expertise covers all relevant areas in cancer research. The competency centre and operational hub for research funding is the Scientific Office.

An experienced team

In the context of a reorganization of the SCL in 2013, an additional department was created out of the Scientific Office. The Scientific Office, which is also the home of the SCR head office, is responsible for calls for proposals and the grant application review process as well as financial controlling and quality control of the funded research projects. The Scientific Committee and the Scientific Office work for both the SCL and the SCR. Thanks to this synergy, administrative expenses can be kept low and charitable donations can be used efficiently. Where needed, the Scientific Office also provides its know-how and its resources to partner organizations such as the foundation SWISS BRIDGE or the CCL, which carry out their research funding more or less independently of the SCL and the SCR.

The new department that was formed is the Science & Development department. In addition to medical-scientific support, another focus of this new department is the development of research studies on important topics. One example is the study "Equal and Secured Access to Cancer Drugs for Off-Label Use", which was conducted for the SCL by the independent consulting group INFRAS and presented in June 2013. The study quantified the extent of inconsistent reimbursement and thus the unfair distribution of access to off-label drugs in oncology. It also outlined approaches that could be applied in order to standardize medical benefit assessment and to regulate the reimbursement of these treatments by the health insurance companies in a uniform manner nationwide.

20.4 million francs for cancer research

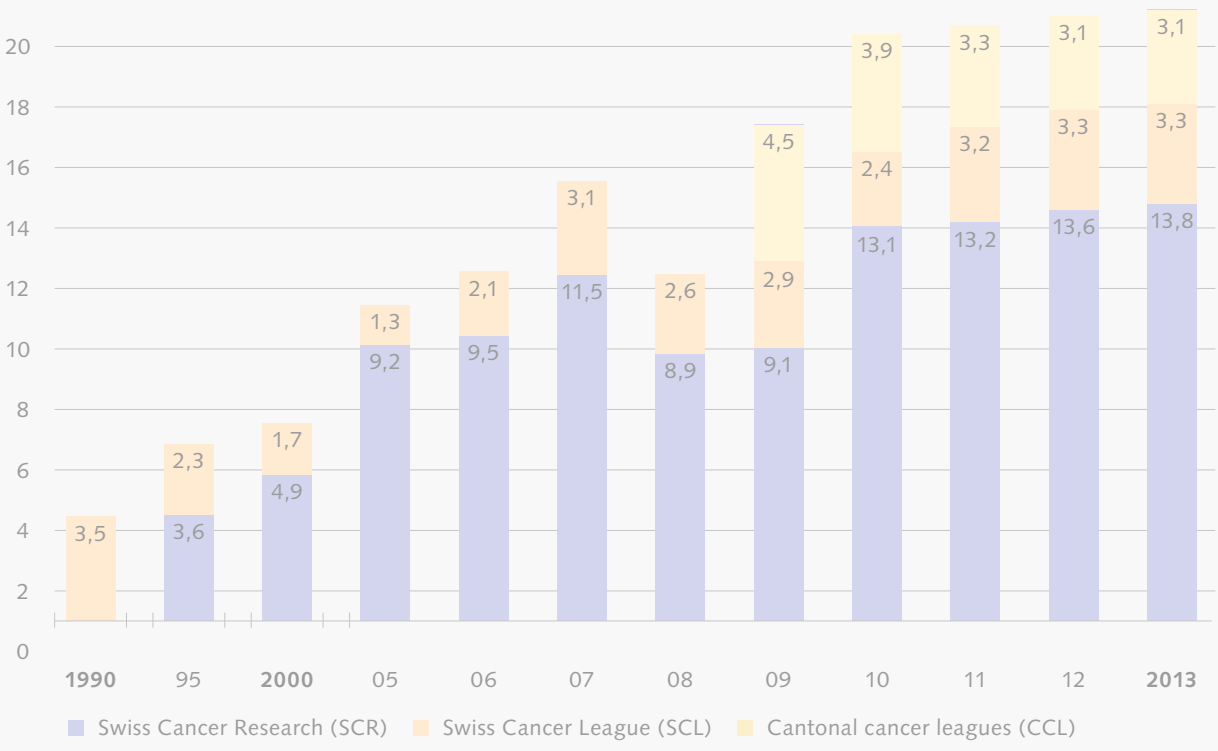
In 2013 the SCR and the SCL provided 17.1 million francs for 80 research projects, bursaries, and research organizations as well as 10 national and international projects and organizations (Figure 1). If we add their contributions to scientific conferences and workshops, which were not included in that figure, the total increases to 17.2 million francs. As in previous years, 80 % of the funds came from the SCR and 20 % from the SCL. In addition to this, the CCL supported a total of 53 research projects and institutions with a total of 3.1 million francs in funding. The resulting overall total for the year 2013 was 20.4 million francs for cancer research projects and activities – approximately the same as the total funding in 2012 (20.2 million francs).

Distribution of cancer research spending

Although the total amount of cancer research funding by the SCR and the SCL in 2013 remained almost the same as in 2012, there were changes in the distribution of the spending (Table 1). Once again, in 2013 most of the funding – 74 % – went to independent research projects, but the amount in this funding area was about 1.5 million francs less than in 2012. The amount of funding given to six Swiss research organizations for basic services increased by 315,000 francs and was 12 % of the total amount of cancer funding; 7 % went to persons receiving bursaries, which was 55,000 francs more than in 2012, and 1 % went to scientific conferences, meetings, and workshops.

Funding contributions going to national and international projects and organizations, which made up 6 % of total funding in 2013, are shown here separately in the overview for the first time. The SCR and the SCL each contributed 150,000 francs to the international CONCORD-2 study, which is examining global trends and geographic differences in survival for 10 cancers. The SCR provided 150,000 francs in funding to the European Organisation for Research and Treatment of Cancer (EORTC). The SCL gave 168,000 francs in support to selected projects and programmes to fight cancer in developing countries, which included 100,000 francs to the programme *Global Access to*

Figure 1
Cancer research funding by SCR, SCL and CCL (independent research projects, bursaries, programme research, research organizations, national and international projects and organizations) since the founding of SCR in 1990.
Not included in these figures are funds for conferences, workshops, etc. Research funding by the CCL has been recorded centrally and published in this report only since 2009.



Pain Relief Initiative (GAPRI) of the Union for International Cancer Control (UICC). In Switzerland the SCR provided 300,000 francs in co-funding for implementation of the National Cancer Programme 2011–2015 (NCP II), and the SCL contributed 100,000 francs towards operating and building cord blood banks.

The distribution of the funds to the cantons was similar to the prior year: At 94 %, the majority of the funds went to the five universities and university hospitals in Basel, Bern, Geneva, Lausanne and Zurich (Figure 2). The largest increase in per cent of the overall total in 2013 was for funds given to Zurich (+10 %). Other changes were in the funding going to Basel (–6 %) and Lausanne (–5 %), whereas funding going to Bern and Geneva remained almost constant (+1 %). The remaining 6 % of the funding went primarily to the Canton of Ticino and the Canton of St. Gallen; smaller sums were given to the following cantons: Aargau, Freiburg, Thurgau, and Wallis.

Tough competition in the independent research projects area

In 2013 the level of competition for the limited funding available for grants for independent project research remained unchanged, especially since even more grant applications were submitted than in the record year of 2012 and for this funding area the total funding available was less than in 2012 (Table 2). Of the 173 grant applications submitted, the SCR and the SCL funded 63 research projects for a total of 12.7 million francs. Relative to the number of grant applications submitted, this is a grant approval success rate of 36 %, which is at about the same level as in 2012 (39 %). The monetary grant success rate – the amount of fund granted relative to the amount of funds requested – was relatively low: Only 33 % of the requested funds could be granted (31 % in 2012). The workload of the members of the Scientific Committee was somewhat reduced, thanks to the addition of two committee members, from 15 to 17: The average number of grant applications reviewed by each member decreased from 23 grant applications in 2012 to 21 applications in 2013.

Table 1
Research funding by SCR and SCL in overview

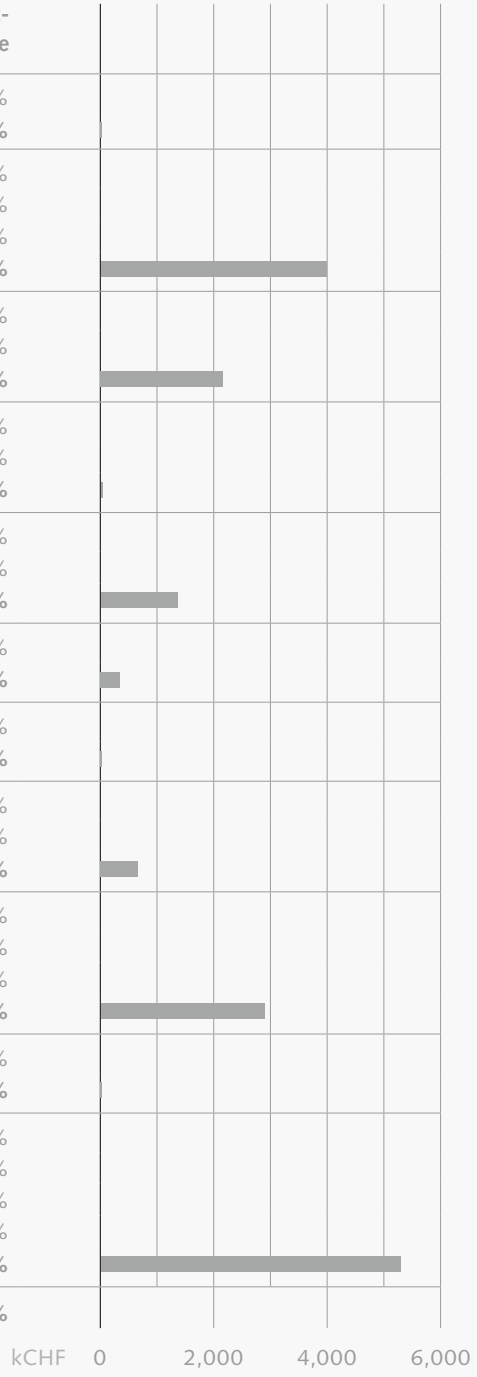
Number of grant applications and amount applied for; number of grants and amounts granted in 2013 (all funding areas)

	Independent research projects	Bursaries	Research organizations	Projects/ org.[1]	Projects/ org.[2]	Conferences, workshops, etc.	**Total**
SCR							
Number of grants approved	50	7	6	2	1	9	**75**
Amount granted in kCHF	10,342	890	1,975	300	300	49	**13,856**
Proportion of total funding	75 %	7 %	14 %	2 %	2 %	0 %	**100 %**
SCL							
Number of grants approved	13	3	1	6	1	23	**47**
Amount granted in kCHF	2,368	372	100	318	100	128	**3,386**
Proportion of total funding	70 %	11 %	3 %	9 %	3 %	4 %	**100 %**
Total SCR and SCL							
Number of grant applications	173	11	7	8	2	32	**233**
Number of grants approved	63	10	7	8	2	32	**122**
Amount applied for in kCHF	38,164	1,316	2,075	618	400	204	**42,777**
Amount granted in kCHF	12,710	1,262	2,075	618	400	177	**17,242**
Proportion of total funding	74 %	7 %	12 %	4 %	2 %	1 %	**100 %**

[1] International projects and organizations [2] National projects and organizations

Figure 2
Distribution of cancer research funding to the cantons by CRS and SCL in 2013

Canton		Number of projects	Amount in kCHF	Percentage
AG	Cantonal Hospital	2	10	100 %
	Total	**2**	**10**	**0 %**
BE	SAKK/IBCSG/SPOG/SCCR	7	1,928	48 %
	University/University Hospital	10	1,166	42 %
	Bursaries	3	402	10 %
	Total	**20**	**3,996**	**24 %**
BS	FMI	1	3	0%
	University/University Hospital	14	2,142	100%
	Total	**15**	**2,145**	**13%**
FR	HES-SO	1	34	87%
	Research award	1	5	13%
	Total	**2**	**39**	**0%**
GE	University/HUG	11	1,142	84%
	Bursaries	2	220	16%
	Total	**13**	**1,362**	**8%**
SG	Cantonal Hospital	6	336	100%
	Total	**6**	**336**	**2%**
TG	Research award	1	5	100%
	Total	**1**	**5**	**0%**
TI	IELSG	1	200	29%
	IOSI/IRB	4	484	71%
	Total	**5**	**684**	**4%**
VD	EPFL	7	1,051	36%
	University/CHUV	7	1,565	54%
	Bursaries	2	277	10%
	Total	**16**	**2,893**	**17%**
VS	Research award	1	10	100%
	Total	**1**	**10**	**0%**
ZH	NICER	1	250	5%
	ETHZ	2	475	9%
	University/University Hospital	28	4,210	79%
	Bursaries	3	362	7%
	Total	**34**	**5,297**	**32%**
	Total	**115**	**16,777**	**100%**



Abbreviations

BE SAKK = Swiss Group for Clinical Cancer Research
IBCSG = International Breast Cancer Study Group
SPOG = Swiss Paediatric Oncology Group
SCCR = Swiss Childhood Cancer Registry

BS FMI = Friedrich Miescher Institute

FR HES-SO = University of Applied Sciences and Arts Western Switzerland

GE HUG = Geneva University Hospital

TI IELSG = International Extranodal Lymphoma Study Group
IOSI = Oncology Institute of Southern Switzerland
IRB = Institute for Research in Biomedicine

VD EPFL = Swiss Federal Institute of Technology Lausanne
CHUV = Lausanne University Hospital

ZH NICER = National Institute for Cancer Epidemiology and Cancer Registration
ETHZ = Swiss Federal Institute of Technology Zurich

Table 2
Distribution of funds by SCR and SCL for independent research projects

	2012	2013	Change compared to prior year
Basic biomedical research			
Number of grant applications	87	92	+6 %
Amount applied for in kCHF	25,241	21,382	−15 %
Percentage of requested funds	55 %	56 %	+1 %
Number of grants approved	31	26	−16 %
Amount granted in kCHF	7,190	5,624	−22 %
Percentage of granted funds	51 %	44 %	−7 %
Grant application number success rate	36 %	28 %	−8 %
Monetary grant success rate	29 %	26 %	−3 %
Clinical research			
Number of grant applications	58	61	+5 %
Amount applied for in kCHF	14,920	13,141	−12 %
Percentage of requested funds	32 %	34 %	+2 %
Number of grants approved	20	25	+25 %
Amount granted in kCHF	4,146	5,096	+23 %
Percentage of granted funds	29 %	40 %	+11 %
Grant application number success rate	34 %	41 %	+7 %
Monetary grant success rate	28 %	39 %	+11 %
Psychosocial research			
Number of grant applications	12	11	−8 %
Amount applied for in kCHF	2,727	2,017	−26 %
Percentage of requested funds	6 %	5 %	−1 %
Number of grants approved	5	6	+20 %
Amount granted in kCHF	693	1,000	+44 %
Percentage of granted funds	5 %	8 %	+3 %
Grant application number success rate	42 %	55 %	+13 %
Monetary grant success rate	25 %	50 %	+25 %
Epidemiological research			
Number of grant applications	13	9	−31 %
Amount applied for in kCHF	3,222	1,624	−50 %
Percentage of requested funds	7 %	4 %	−3 %
Number of grants approved	10	6	−40 %
Amount granted in kCHF	2,134	990	−54 %
Percentage of granted funds	15 %	8 %	−7 %
Grant application number success rate	77 %	67 %	−10 %
Monetary grant success rate	66 %	61 %	−5 %
All projects			
Number of grant applications	170	173	+2 %
Amount applied for in kCHF	46,110	38,164	−17 %
Number of grants approved	66	63	−5 %
Amount granted in kCHF	14,163	12,710	−10 %
Grant application number success rate	39 %	36 %	−3 %
Monetary grant success rate	31 %	33 %	+2 %

(percentage of funds)

As in previous years, the greatest competition for funding was in the basic biomedical research area, even though once again, basic biomedical research received the largest part (44 %) of the funds for independent project research. In this area the monetary grant success rate in 2013 was lower, at 26 % (29 % in 2012). Clinical research, which comprises both clinical research with patients and also translational research projects, received 40 % of the funding, and the monetary success rate in this area increased to 39 % (28 % in 2012).

Compared to the prior year, there were also changes in 2013 in the funding and the success rates in the epidemiological and psychosocial research areas. However, the numbers already fluctuate in these areas each year due to the relatively small number of grant applications that are submitted and approved. In 2013, 8 % of the funding went to each of these two areas of research. In psychosocial research the monetary grant success rate rose to 50 % (25 % in 2012), and in epidemiological research it fell to 61 % (66 % in 2012). The grant approval success rates were 28 % for basic biomedical research, 41 % for clinical research, 55 % for psychosocial research, and 67 % for epidemiological research.

Good-quality projects that could not be funded

In the funding area of independent research projects, one category of grant applications is a particular problem – not only for the researchers but also for the funding institutions: "approved but not funded" (ABNF) projects. These are grant applications that the Scientific Committee deemed high quality and approved for funding but that the boards of the SCR and the SCL could not fund due to lack of monies. On the part of many researchers who are notified of the ABNF status of their projects there is frustration and a lack of understanding, often more so than when an application is rejected for funding.

Of the 173 grant applications submitted in 2013, the number of ABNF research projects was 28, or five research projects fewer than in 2012. Of the 28, 23 were in basic biomedical research, and five were in clinical research. As in 2012, in the areas of psychosocial and epidemiological research, all projects approved for funding by the Scientific Committee were funded in 2013. The relatively high percentage of ABNF grant applications, 16 % of all grant applications submitted, is spurring the funding institutions on to generate even more monies for the funding of high-quality research projects. One way to do this

Table 3
Distribution of funds by SCR and SCL for independent research projects by research area and year, 2004–2013

	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013
Basic biomedical research										
Total in million CHF	6.00	4.18	5.14	6.12	4.35	4.80	7.00	7.56	7.19	5.62
Percentage of total amount	56 %	49 %	52 %	56 %	48 %	47 %	59 %	54 %	51 %	44 %
Clinical research										
Total in million CHF	3.31	3.36	3.31	3.85	2.90	3.96	3.14	4.56	4.15	5.10
Percentage of total amount	31 %	40 %	34 %	35 %	32 %	39 %	26 %	32 %	29 %	40 %
Psychosocial research										
Total in million CHF	1.00	0.61	0.74	1.05	0.84	0.70	0.36	0.93	0.69	1.00
Percentage of total amount	9 %	7 %	7 %	9 %	9 %	7 %	3 %	7 %	5 %	8 %
Epidemiological research										
Total in million CHF	0.37	0.31	0.74	0.00	0.93	0.74	1.40	1.03	2.13	0.99
Percentage of total amount	4 %	4 %	7 %	0 %	11 %	7 %	12 %	7 %	15 %	8 %
All projects										
Total in million CHF	10.68	8.46	9.93	11.02	9.02	10.20	11.90	14.08	14.16	12.71

Sandzeichnung, Videostill, 2012

that has been a positive development in recent years is targeted fund raising with other foundations, which then contribute all or some of the costs of selected research projects. Thanks to these project-specific donations, additional research projects that were quality-tested by the Scientific Committee can be funded that are a good match for other foundations with regard to the research topics and aims.

Funding for patient-centred research

In addition to the quality of the research projects – which is the central criterion in funding – an important priority in the funding strategy of the SCR and the SCL is targeted support for patient-centred research. Patient-centred research aims at continuous improvement of medical care and psychosocial support for persons with cancer. For example, treatment optimization studies in clinical research aim to find the optimal combination and sequence of treatment options. Another example is psychosocial research that investigates ways to improve the quality of life of patients and their families. Nursing research, health services research, and many epidemiological studies also aim at direct benefit to patients and their families.

For more than 10 years, allocation rules have been utilized as an instrument for the promotion of patient-centred research. Within the funding area of independent research projects, 60 % of the funding is earmarked for patient-centred research, broken down into 40 % for clinical research and 20 % for research studies in the psychosocial area, epidemiol-

ogy, nursing sciences, public health, and so on. The remaining 40 % of the funding for independent research projects goes to basic biomedical research. In 2013, the distribution of funds for independent research was 44 % for basic biomedical research and 56 % for patient-centred research (Table 3).

Support of research organizations

A further instrument for promoting patient-centred research is financial support for basic services that established Swiss research organizations perform for the benefit of clinical and epidemiological research in Switzerland. In clinical research, which is very costly in terms of time and resources, these services include designing study protocols, coordinating national and international multicentre studies, and administrative tasks for the study approval process with Swissmedic and the ethics committees. In the area of cancer epidemiology, the organizations supported by the SCR and the SCL provide researchers with know-how and resources for collecting, managing, and analysing data in the cantonal and national cancer registries.

The SCR uses a maximum of 20 million francs of the yearly research funding budget for targeted support of five to six research organizations that for years have been performing central and indispensable services for Swiss cancer research. Their basic services are funded based on performance agreements that define in a clear and binding way the objectives for research and the requirements with regard to reporting and evaluation. In addition, the condition is that the institutions must secure their financing long-term on their own and independently of these contributions. In 2013 the SCR supported six research organizations with a total of 2 million francs. Another 100,000 francs were provided by the SCL (Table 4).

Funding by the cantonal cancer leagues

In 2013 the amount of funding given to research projects and institutions in the cantons by the cantonal cancer leagues remained practically unchanged: A total of 3.1 million francs was given to 53 research projects (Table 5). The by-far largest sum of 1.2 million francs – 39 % of the total funding by the CCL for research – was given once again by the Geneva Cancer League. The Zurich Cancer League provided 20 % of the funding, followed by the Bern Cancer League (14 %), the Cancer League of both cantons of Basel (10 %), and the Cancer League of Ticino (9 %). The remaining 8 % was given by the Cancer League of Thurgau and the cancer leagues of Eastern and Central Switzerland. Of the 19 cantonal cancer leagues in total, 11 did not fund cancer research in 2013, since for the majority of the cantonal cancer leagues, funding research is not a priority task. The research projects and institutions supported by the CCL are presented from pages 44 to 63.

Table 4
Supported research organizations

Funding by SCR, according to performance agreement by research organization and year, 2009–2013

Amount in kCHF

	2009	2010	2011	2012	2013
Swiss Group for Clinical Cancer Research (SAKK)	600	600	600	600	900*
International Breast Cancer Study Group (IBCSG)	560	560	560	560	500
National Institute for Cancer Epidemiology and Cancer Registration (NICER)	–	–	200	200	250
International Extranodal Lymphoma Study Group (IELSG)	–	–	–	200	200
Swiss Paediatric Oncology Group (SPOG)	100	100	100	150	150
Swiss Childhood Cancer Registry (SCCR)	–	–	50	50	75
Total	**1,260**	**1,260**	**1,510**	**1,760**	**2,075**

* of which 100,000 francs were from the SCL

Table 5
Research funding by the cantonal cancer leagues in overview

Number of research projects and institutions supported and amount granted in 2013 in comparison with prior year 2012

Cancer league	Number of projects and institutions supported 2012	Number of projects and institutions supported 2013	Change compared to 2012 (absolute)	Amount granted 2012 in kCHF	Amount granted 2013 in kCHF	Change compared to 2012 (relative)
Aargau	1	0	–1	60.0	0.0	–
Basel	10	10	0	280.0	300.0	+7 %
Bern	9	9	0	490.0	438.0	–11 %
Central Switzerland	2	1	–1	110.0	50.0	–55 %
Eastern Switzerland	2	1	–1	120.0	100.0	–17 %
Geneva	12	14	+2	1,131.9	1,234.5	+9 %
Grisons	1	0	–1	5.0	0.0	–
Neuchâtel	1	0	–1	144.0	0.0	–
Thurgau	2	3	+1	33.0	112,0	+239 %
Ticino	4	5	+1	210.0	268.0	+28 %
Zurich	9	10	+1	551.5	642.2	+16 %
Total	**53**	**53**	**0**	**3,135.4**	**3,144.7**	**0** %

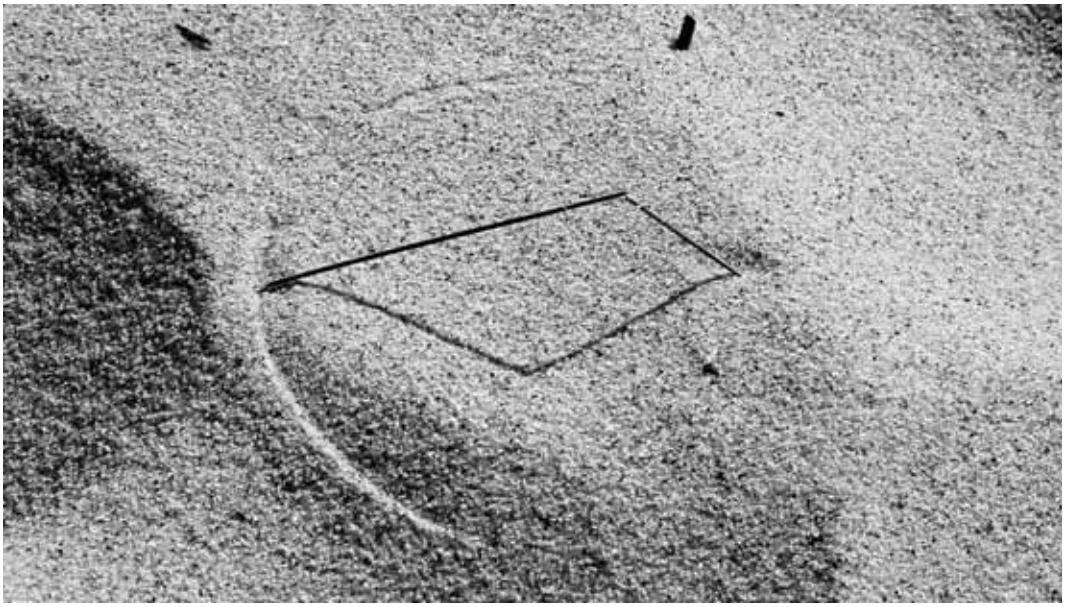
The research organizations supported in 2013 in brief

Swiss Group for Clinical Cancer Research (SAKK)
SAKK is a decentralized academic research institute that has conducted clinical studies on cancer treatment in all larger hospitals in Switzerland since 1965. SAKK encompasses a wide network of about 20 Swiss research groups and a coordination centre in Bern. For rare cancers SAKK works together with selected collaborative groups in other countries. SAKK aims to improve cancer treatment, study the effectiveness and tolerability of new treatments (radiotherapy, chemotherapy, surgery), and establish new treatment standards. In 2013 nearly 1000 adult patients participated in 44 clinical studies conducted by SAKK. As an independent and non-profit organization, SAKK pursues no commercial interests.

International Breast Cancer Study Group (IBCSG)
Since 1977 the IBCSG has conducted academic clinical trials with the aim to support breast cancer research, coordinate international research activities, and improve the treatment of women with breast cancer. The IBCSG is a multicentre study group with a coordination centre located in Bern, a data management centre and a statistics centre in the United States, and a pathology reference laboratory in Italy that serves the entire organization. In Switzerland, all university clinics, numerous cantonal and other hospitals, and oncologists in private practices participate in IBCSG studies. In 2013 250 patients participated in seven clinical studies conducted by the IBCSG.

National Institute for Cancer Epidemiology and Cancer Registration (NICER)
NICER promotes and supports population-based cancer registration and epidemiological cancer research in Switzerland. As a national coordination centre, NICER harmonizes the work of the 20 cantonal and regional cancer registries. It compiles the cancer data collected in the cantons, assures the quality of the data, and analyses the data at the national level. These data collected in the network are utilized to determine national statistics on cancer incidence, mortality, and survival rates. This work aims to make possible evidence-based decision making both in health care policy and in clinical medicine that will benefit the health of the population and also individual patients with cancer.

International Extranodal Lymphoma Study Group (IELSG)
The IELSG, a multicentre study group, was created in 1998 in Ascona, and its coordination and data management centre is in Bellinzona. It aims to foster research in the area of extranodal lymphomas (ENL) and to coordinate international research activities. As these lymphomas develop from all organs and sites in the body, different treatments are required, and their effectiveness has to be analysed separately. To obtain a sufficient number of cases, multicentre studies are necessary. At present there are more than 200 international institutes in this network. In 2013 the IELSG coordinated nine clinical studies with more than 200 participants.



Sandzeichnung, Videostill, 2012

Swiss Paediatric Oncology Group (SPOG)
SPOG has been conducting clinical and epidemiological cancer research in paediatric oncology for 35 years, with the aim to improve treatment and quality of life of children and adolescents with cancer. The SPOG is a national, independent association located in Bern. Belonging to the SPOG are all paediatric oncology departments at Swiss hospitals and the Swiss Childhood Cancer Registry. As childhood cancer is relatively rare, research in childhood cancer is possible only in the framework of international collaborations. At present, more than 20 SPOG clinical studies are ongoing, with approximately 150 patients participating.

Swiss Childhood Cancer Registry (SCCR)
The SCCR is the national cancer registry for children and adolescents in Switzerland. Since 1976 it has collected data on all new cases of cancer in young persons up to the age of 20. It also documents treatments and conducts longitudinal studies on health and quality of life of childhood cancer survivors. In this way it contributes towards research on the causes of childhood cancer, improvement of cancer treatment, and prevention of late effects in cancer survivors. The SCCR, which is funded from several sources, is located at the Institute of Social and Preventive Medicine at the University of Bern and works closely with the SPOG. Up to now, the SCCR has collected data on 9300 children and adolescents with cancer.

Overall, the SCR, SCL, and the CCL gave 20.4 million francs to cancer research in 2013, which was 1 % more than in 2012 (Table 6). This sum supported a total of 175 research projects, bursaries, research organizations, and conferences and workshops. Two-thirds of the monies was contributed once again by the SCR, 17 % by the SCL, and 15 % by the CCL. The increase in the figures for the funding area "Other" was primarily for two reasons: First, in 2013 there were significant, one-time contributions to large international studies (CONCORD-2), and second, for the first time, the figures here also include the contributions to national projects and organizations, in particular for Oncosuisse and implementation of the National Strategy Against Cancer 2014–2017.

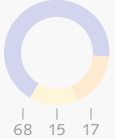
Table 6
Research funding by SCR, SCL, and CCL in overview

Number of grants approved and amount granted in 2013 and change compared to prior year 2012 (all funding areas)

	Independent research projects		Bursaries		Research organizations		Other*		**Total**	
SCR										
Number of grants approved	50	−2 %	7	−13 %	6	0 %	12	+50 %	**75**	+3 %
Amount granted in kCHF	10,342	−6 %	890	+8 %	1,975	+12 %	649	+233 %	**13,856**	+1 %
SCL										
Number of grants approved	13	−13 %	3	+50 %	1	–	30	+114 %	**47**	+52 %
Amount granted in kCHF	2,368	−25 %	372	+284 %	100	–	546	+680 %	**3,386**	+2 %
CCL										
Number of grants approved	53	0 %	–	–	–	–	–	–	**53**	0 %
Amount granted in kCHF	3,145	0 %	–	–	–	–	–	–	**3,145**	0 %
Total SCR, SCL and CCL										
Number of grants approved	116	−3 %	10	+0 %	7	+17 %	42	+91 %	**175**	+11 %
Amount granted in kCHF	15,855	−8 %	1,262	+37 %	2,075	+18 %	1,195	+351 %	**20,387**	+1 %

Change compared to 2012

* Funding for national and international projects and organization, conferences, workshops etc.



(percentage of funds)

Once more we extend sincere thanks to all of the charitable donors, whose generous and loyal support makes these excellent results benefitting cancer research and patients possible.

Rolf Marti, PhD
Rolf Marti has headed the Scientific Office and the Science & Development department since 2003. He is a member of the managing board of the Swiss Cancer League and director of the Swiss Cancer Research foundation. As a member of the core group of the National Strategy Against Cancer 2014–2017, one of the current focuses of his work is implementation of the fields for action "Research promotion" and "Epidemiology and monitoring".
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Excellent marks for research funding

The Swiss Cancer Research foundation (SCR) and the Swiss Cancer League (SCL) perform excellent work in cancer research funding in Switzerland. They fund research projects of high quality producing many significant publications as output – with top ratings in an international comparison. These are the findings of an independent, externally conducted evaluation. At the same time, the evaluation identified valuable potential for improvement for diverse evaluation criteria.

The board of the SCR foundation and the board of the SCL commissioned an extensive evaluation of their research funding activities in 2012/2013. The company evalueSCIENCE was asked to evaluate the publications of funded research projects, the quality and efficiency of the research funding, the organs involved, and the governance, processes, and structures. The evaluation was based on the time period from 1998 to 2012 and on international standards (method: "informed peer review" following the Zurich Model, an evaluation method developed at the University of Zurich). The last evaluation of the research funding activities of the SCR and SCL had been conducted in 1997.

The starting point was a comprehensive self-evaluation report prepared by the Research Funding Department. The evaluation carried out by evalueSCIENCE had three main foci: bibliometric analysis of the scientific publications, an online survey of grant applicants, and an evaluation by an independent group of experts (peers).

Bibliometrics: excellent output

How good a research paper is and what its impact is within a particular field of research is mainly assessed based on two factors: the journals in which the paper is published (impact factor) and how often the paper is cited in other publications (citations). The more prestigious the journal is and the higher the number of citations, the more significant the paper is. More than 400 research projects funded by SCR/SCL in the period from 1998 to 2006 were appraised quantitatively and qualitatively.

The most important results:

– SCR and SCL funded research projects of excellent quality. Especially projects in basic biomedical research, epidemiological research, and laboratory-oriented clinical research resulted in publications of great-to-very great scientific significance in the particular research area. The funding efficiency that is, the financial investment per publication was also the highest for these three funding areas.

Stéphanie Buvelot Frei, PhD
Scientific assistant in the Scientific Office, Swiss Cancer League and Swiss Cancer Research foundation, Bern

Kurt Bodenmüller, lic. phil. nat.
Communications manager of the Scientific Office, Swiss Cancer League and Swiss Cancer Research foundation, Bern

– In comparison, scientific output and funding efficiency were lower for patient-centred research. This can be attributed to the fact that clinical studies are much more difficult and more expensive, and there is also a longer lag time between research funding and publishable results.
– Less highly rated were psychosocial research projects, whereby it should be mentioned that the different research areas should not be directly compared to one another. Publications in this field of research have a lower impact factor than papers in basic biomedical research, for example.
– In a further analysis, approved research projects were compared to a randomly selected sample of grant applications not approved for funding and grant applications that the Scientific Committee deemed high quality and approved for funding but that could not funded due to lack of monies (approved but not funded, ABNF). Approved projects clearly outperformed the projects not approved for funding and somewhat outperformed the ABNF projects.
– Finally, the results of the projects funded by the SCR and SCL were compared with publications put out by research projects funded by nine comparable funding organizations in Northern Europe (basis: Web of Knowledge database). The highest number of citations per publication was achieved by papers put out by projects funded by the SCR/SCL – which evalueSCIENCE deems a very favourable result. Also excellent in this comparison was the funding efficiency.

Survey: positive feedback

As a part of the evaluation, 457 applicants who had submitted research proposals in the last five years were invited to take part in an online survey on the quality of the submission and review process. Of the 242 researchers (53 %) that participated, 154 (64 %) had research proposals that were approved for funding in the time period, 70 (29 %) had proposals that were not approved, and 18 (7 %) had proposals that were approved but could not be funded (ABNF).

The most important survey results:
– Approximately 70 % of the applicants felt that the SCR and SCL are important-to-very important for their research activities, and over 80 % find the SCR and SCL positive-to-very positive for cancer research in Switzerland altogether.
– The grant application review process was found to be transparent, fair, and qualitatively good by 86 % of the applicants.
– Approximately 30 % of the applicants whose proposals were not approved or were ABNF found the grant application review process to be not transparent and not fair. For many of the researchers affected, receiving an ABNF decision led to a greater lack of understanding and more frustration than receiving a not approved for funding decision.
– 98 % of the applicants appreciated the support provided by the Research Funding Department in the context of the grant application process.

Group of experts: quality is central

The main part of the evaluation was an all-day site visit at the Research Funding Department by a group of six independent, internationally renowned experts (see box "Members of the group of experts"), who conducted five qualitative interviews with central actors at SCR, SCL, the Scientific Committee, applicants, and partner organizations. The peers focused their evaluation on the following criteria: strategy, research support, and quality assurance as well as governance, structures, and resources. In their report, the peers underlined the important function of SCR and SCL as funding organizations for cancer research in Switzerland. They made particular mention of the excellent work of the Scientific Committee in reviewing grant applications.

Based on the peers' report, evaluSCIENCE worked out several recommendations:

- The aim of supporting research projects of the best quality should remain the highest strategic priority. In addition, a common strategy and strategic guidelines should be developed for the research funding by the SCR, SCL, and the cantonal cancer leagues (CCL).
- The 40-40-20 rule, according to which the funds should be allocated to the different fields of research, should be re-evaluated. (Within the funding area of independent research projects, the funding is allocated as follows: 40 % for clinical research, 20 % for research studies in the psychosocial area, nursing sciences, and epidemiology, and 40 % for basic biomedical research.)
- The experts submitted a suggestion for discussion: 70 % of the funds could be earmarked for the qualitatively best proposals within independent research projects and 30 % for specific, strategic research topics (such as funding for participation in international clinical studies, funding for neglected niche areas).
- To optimize reporting by researchers (in papers, reviews, book chapters) it would advisable to develop appropriate incentives and a tougher reporting control. This would also improve the visibility of the funding organizations.
- Communication with grant applicants, especially communication of non-approval or ABNF decisions), should be optimized, so as to make negative decisions better understood.

Measures implemented

The Scientific Committee, the board of the SCR foundation, and the board of the SCL studied and discussed the evaluation report extensively. The mostly very good results affirm the organizations in their efforts to support excellent research that leads to advances in treatment and in the fight against cancer and that helps to improve patients' survival rates and quality of life. For this reason, also in the future 70 % to 80 % of the research funding will go to competitive, independent research projects.

Based on the feedback from the grant applicants and the experts' recommendations, changes have already been made to various terms and conditions of grant application submission and review processes. Starting in 2014, the maximum amount of funding granted per research project has been raised from CHF 250,000 to CHF 375,000 and the duration increased from three to maximum four years. In addition, the researchers are now allowed to use more grant money for consumables, which gives them more flexibility in their budget use. Although it is still the case that a researcher may be the principal applicant of at most one ongoing project, there is no longer a restriction on the number of projects as a co-applicant.

Further measures decided on by the Scientific Committee serve to simplify the submission of grant applications (limiting the documents to be submitted) and optimize the review process (two external reviewers per grant application). In addition, priority will be given to supporting research projects that are rated "clearly cancer-relevant". To improve reporting, the grant recipients are obligated, under the terms of the written funding agreement, to mention the SCR or SCL in all publications resulting from the projects.

Two measures aid at improving transparency and communication with grant applicants: The review criteria and the steps in the review process are now described clearly and openly in the information sheet accompanying the application documents. Also, along with the letter notifying the applicant of the funding decision, the applicant now also receives information on their position in the ranking list of reviewed projects and statistical information on the number of applications submitted, the amount applied for, the number of grants approved, and the amount granted.

Research funding strategy

Implementing the experts' recommendations regarding governance and structures will take some time. As to revising the research promotion rules and regulations, two goals stand in the foreground: The responsibilities of and cooperation between the board of the SCR foundation and the board of the SCL at the institutional level should be more clearly defined. In addition, research funding by the SCL and by the relevant CCL should be more closely coordinated. A first step towards improving cooperation with the CCL has already been taken: After each

round of submissions the CCL are to be informed about all research projects in their cantons that are being funded by the SCR and SCL. In the longer term, a common research funding strategy will be developed that takes into consideration the specific characteristics of the SCR, SCL, and the CCL. Taking into account overarching national goals and the priorities of the "National Strategy Against Cancer 2014–2017", the activities for funding high-quality and patient-centred cancer research are to be harmonized and optimized.

Members of the group of experts

- Prof. Denis Monard, PhD, former president of the Swiss Academy of Sciences (SCNAT) and former director the Friedrich Miescher Institute for Biomedical Research (FMI), president of the group of experts, Basel
- Prof. Stanley B. Kaye, MD, head of the Drug Development Unit and head of the Section of Medicine at the Royal Marsden Hospital and the Institute of Cancer Research, London
- Denis Lacombe, MD, director headquarters, European Organization for Research and Treatment of Cancer (EORTC), Brussels
- Prof. Jürg Schifferli, MD, PhD, former member of the National Research Council of the Swiss National Science Foundation (SNSF), dean of research at the Faculty of Medicine, University of Basel, Basel
- Prof. Emile Voest, MD, head of the Department of Medical Oncology, University Medical Center Utrecht, and chair of the Scientific Advisory Board of the Dutch Cancer Society, Amsterdam
- Prof. Otmar D. Wiestler, MD, Dr. h.c., chairman of the scientific board of the German Cancer Research Center (DKFZ), and member of the board of German Cancer Aid, Bonn

Stéphanie Buvelot Frei, PhD
Stéphanie Buvelot Frei has a doctorate in cell biology and worked for many years in the United States, Lausanne, and Zurich in cell and molecular biology basic research in the area of cancer. From 2005 to 2010 she worked as a scientific assistant at ETH Zurich. She has been a scientific assistant in the Scientific Office of the Swiss Cancer League and the Swiss Cancer Research foundation since 2011.
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Kurt Bodenmüller, lic. phil. nat.
Kurt Bodenmüller is a microbiologist who has worked in the field of science communications since 1997. He worked for many years as a consultant at an international PR company. He has been communications manager of the Scientific Office of the Swiss Cancer League and the Swiss Cancer Research foundation since 2008.
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Partner organizations and committees

Swiss Cancer Research foundation (SCR)

In existence since 1990, the Swiss Cancer Research foundation generates donations that help provide funding for all areas of cancer research: basic, clinical, epidemiological, and psychosocial research. A special focus is the funding of patient-centred research projects that result as far as possible in direct patient benefit. The SCR foundation board, presided over by Prof. Thomas Cerny, MD, is responsible for distributing the funds to the researchers. The funding decisions are based on the recommendations made by the Scientific Committee. The Scientific Committee, made up of recognized experts in cancer research and medicine, reviews the grant applications according to clearly defined criteria. The SCR also supports the development and implementation of measures to fight cancer in Switzerland – namely, the National Cancer Programme 2011–2015.

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Swiss Cancer League (SCL)

The Swiss Cancer League (SCL) aims for a world where fewer persons get cancer, fewer persons suffer the consequences of and die of cancer, more persons are cured of cancer, and persons with cancer and their families receive care and support in all phases of cancer and in dying. As the national umbrella organization with headquarters in Bern, the SCL brings together 19 cantonal and regional cancer leagues. A non-profit organization financed mainly through donations, the SCL is Switzerland's competence centre for cancer. It supports the cantonal cancer leagues through knowledge transfer, provision of services, developments, and coordination at the national level. It supports cancer research, provides information on risk factors and early detection measures, and runs national cancer prevention programmes. It develops specific continuing education courses for a variety of occupational groups. A number of different advice and support services for persons with cancer and their families and also the SCL brochures are developed in Bern. Responsible for strategic management of the SCL is the SCL board, presided over by Prof. Jakob R. Passweg, MD.

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Cantonal cancer leagues (CCL)

In the 19 cantonal and regional cancer leagues, persons with cancer and their family members receive personal and individual advice from experts on treatment as well as on financial and organizational questions. The personel at the CCL often advise persons over a longer time period and support them in difficult situations. They provide information on legal and insurance issues and help with the reorganization of the clients' social and financial situations. They provide contacts to other support institutions, such as home care organizations. If their illness brings persons with cancer into financial difficulties, they can apply for support payments. The CCL organize group meetings and courses, where persons with cancer can talk about their fears and experiences and can learn to deal with their illness. Some cancer leagues offer specialized psycho-oncology support for children of adults with cancer. And in some cantons there are outpatient oncology care services that support persons with cancer at home.

The CCL are at work in Switzerland and in Liechtenstein. The services offered by the CCL vary in type and extent and depend strongly on the financial and human resources of the individual cancer league as well as on the services made available by other providers.

Cantonal and regional cancer leagues in the German-speaking part of Switzerland and in Liechtenstein

– Aargau Cancer League
– Basel Cancer League
– Bern Cancer League
– Central Switzerland Cancer League
– Eastern Switzerland Cancer League
– Grisons Cancer League
– Liechtenstein Cancer League
– Schaffhausen Cancer League
– Solothurn Cancer League
– Thurgau Cancer League
– Zug Cancer League
– Zurich Cancer League

Cantonal cancer leagues in the French-speaking part of Switzerland and in Ticino

– Fribourg Cancer League
– Geneva Cancer League
– Jura Cancer League
– Neuchâtel Cancer League
– Ticino Cancer League
– Valais Cancer League
– Vaud Cancer League

The board of the Swiss Cancer Research foundation

The board of the Swiss Cancer Research foundation (SCR) is made up of one representative each of the chairmanship of the Swiss Cancer League (SCL), the Swiss Group for Clinical Cancer Research (SAKK), and the Swiss Paediatric Oncology Group (SPOG); one expert each in the different research areas; and independent persons.

The eight members of the SCR foundation board are:

President

Prof. Thomas Cerny, MD
Head physician of Oncology/
Haematology Clinic
Department of Internal Medicine
Cantonal Hospital St. Gallen
Past president of SCL
since 2009

Vice president

Prof. Richard Herrmann, MD
Head of Clinical Research Department
Basel University Hospital
Past president of SAKK and clinical
research representative
since 2009

Prof. Matthias Egger, MD
Member of the Board, Institute
of Social and Preventive Medicine
University of Bern
Epidemiological research representative
since 2009

Erika Forster-Vannini
Former member of the
Council of States
St. Gallen
Independent person
since 2012

Prof. Hans Hengartner, PhD
Langnau am Albis
Basic cancer research representative
since 2009

Eduard Holdener, MD
Therwil
Independent person
since 2009

Treasurer

Gallus Mayer
Banking specialist
Head of Finance and Accounting
Notenstein Private Bank Ltd.
St. Gallen
since 2009

Prof. Nicolas von der Weid, MD
Head of Oncology/Haematology
Department
Co-head physician of Paediatrics
University Children's Hospital Basel
(UKBB)
Past president SPOG and paediatric
research representative
since 2009

The board of the Swiss Cancer League

The highest body of the Swiss Cancer League (SCL) is the delegates' assembly, to which the representatives of the cantonal and regional cancer leagues belong. Strategic management is the responsibility of the board of the SCL. The members of the board represent both different specialties in the fight against cancer and different parts of Switzerland. Prof. Jakob R. Passweg, MD, was elected president of the board in 2010, and PD Gilbert Bernard Zulian, MD, is vice president.

The 11 members of the SCL board are:

President
Prof. Jakob R. Passweg, MD
Head physician of Haematology Clinic
Basel University Hospital
since 2007

Treasurer
Gallus Mayer
Banking specialist
Head of Finance and Accounting
Notenstein Private Bank Ltd.
St. Gallen
since 2009

Vice president
PD Gilbert Bernard Zulian, MD
Head physician of Palliative
Medicine Department
Hôpital de Bellerive
Geneva University Hospital
since 2009

Hans Neuenschwander, MD
Head physician of Palliative Care
Regional Hospital of Lugano
since 2010

Past president
Prof. Thomas Cerny, MD
Head physician of Oncology/
Haematology
Department of Internal Medicine
Cantonal Hospital St. Gallen
since 1998

Markus Notter, MD
Head physician of Radiotherapy
Department
Neuchâtel Hospital
La Chaux-de-Fonds
since 2013

Irène Bachmann-Mettler
Project head, Institute of General
Practice and Health Services Research
University of Zurich
President of Swiss Oncology
Nursing Society
since 2003

Corinne Ullmann
Manager
Schaffhausen Cancer League
since 2013

Prof. Daniel Betticher, MD
Head physician of Oncology
Department
HFR Fribourg, Cantonal Hospital
since 2006

Brigitta Wössmer, PhD
Head psychologist of Psychosomatics
Basel University Hospital
President of Swiss Society of
Psycho-Oncology
since 2011

Lucienne Bigler-Perrotin
Manager
Geneva Cancer League
since 2009

The Scientific Committee

Members of the Scientific Committee 2013 (left to right): Ruth Chiquet Ehrismann (as of 2013), Rolf Marti (head of the Scientific Office), Maria Blettner, Holger Moch, Martin Pruschy, Beat W. Schäfer, Silke Gillessen (as of 2013), Emanuele Zucca (as of 2013), Martin F. Fey (president), Freddy Radtke, Simone Benhamou, Adrian Ochsenbein, Friedrich Stiefel, Hans-Uwe Simon, Jürg Schwaller (as of 2013), Kurt Fritzsche, and Curzio Rüegg (as of 2013) (not pictured: Primo Schär).

The Scientific Committee is responsible for evaluating the research grant applications submitted to the Swiss Cancer Research foundation (SCR) and the Swiss Cancer League (SCL) by researchers seeking research funding. The committee's peer review process uses strictly defined evaluation criteria (see box, "Criteria for high-quality cancer research"). The central criterion is always whether a research project is expected to advance our understanding of cancer prevention, causes, or treatment.

The 17 members of the Scientific Committee are recognized experts with outstanding achievements and expertise in all areas relevant to cancer research. Having all of the research areas represented on one committee prevents the formation of specialized subcommittees and also assures funding of research trends in all areas. The members serve on the committee for three years and can be re-elected twice.

The president of the Scientific Committee is Prof. Martin F. Fey, MD. The committee members are representatives of the following research areas:

- basic biomedical research: 5 members
- patient-centred clinical cancer research: 3 members
- laboratory-based clinical cancer research: 2 members
- epidemiology and cancer prevention: 2 members
- psychosocial and other cancer research (public health research): 2 members
- translational cancer research: 2 members

Each grant application is reviewed by two members of the Scientific Committee. In addition, each application is reviewed by an average of three external peer reviewers. In the year under report, the Scientific Committee reviewed 173 research grant applications, which is three more than in the previous

year. Once again, more than half of the grant applications submitted were in basic research. Thanks to the addition of two more committee members, the yearly reviewing workload of the individual members could be reduced somewhat, from an average of 23 grant applications in 2012 to an average of 21 applications in the reporting year.

The Scientific Committee meets twice a year to discuss at length the grant applications reviewed by the committee members and external reviewers (see box, "The research grant application review process"). Based on the discussions the committee produces a ranked list of the grant applications that the committee recommends to the boards of the SCR and the SCL for grant approval.

As the financial means are limited, it is unfortunately never possible to approve grants for all grant applications that the committee judges to be of good quality and worthy of funding. In the reporting period 2013 there were 28 research grant applications that could not be approved for funding despite their good quality (these projects are designated "approved but not funded", ABNF), this was five grant applications fewer than in the previous year (33 ABNF projects).

Operational support for the Scientific Committee's important tasks and responsibility is provided by the Scientific Office of the SCL and the SCR. It organizes the call for and the review of grant applications and is responsible for quality control of the funded research projects.

Criteria for high-quality cancer research

The quality of research grant applications is evaluated according to the following criteria:

- Cancer relevance: Is the proposed research project expected to contribute important new observations or knowledge on the causes, prevention, or treatment of cancer?
- Originality or socio-economic significance: Is the proposed research project original, innovative (basic research projects), or of socio-economic importance (clinical or epidemiological projects)?
- Choice of methodology: Have the most appropriate methods for the project realization been chosen?
- Feasibility: Is the project feasible in terms of finances, human resources, and organization?
- The applicant's past accomplishments: What are the applicant's (or the project group's) previous scientific achievements? How good were the publications?

The research grant application review process

The grant application is submitted to and recorded by the Scientific Office.
↓
The grant application is sent for review to two members of the Scientific Committee who are experts in the relevant specialist field (such as basic research or psycho-oncology).
↓
The two Scientific Committee members recommend additional experts as external reviewers.
↓
The Scientific Office asks the external reviewers to review the grant application.
↓
The reviewers evaluate the grant application. Four to six reviews are obtained for each research grant application, two of which are by Scientific Committee members.
↓
The Scientific Office collects the reviews and puts them in a file.
↓
The research grant application is discussed in detail at the bi-annual meeting of the Scientific Committee.
↓
After the meeting, the Scientific Office writes up detailed minutes and creates a list of all grant applications ranked according to the committee's recommendations.
↓
The ranking list is forwarded to the boards of the Swiss Cancer Research foundation and the Swiss Cancer League, which then decide which grant applications will be funded.
↓
The Scientific Office notifies the applicant of the decision. The reviews are made available to the applicant in an anonymous form.

Members of the Scientific Committee

President

Prof. Martin F. Fey, MD
Institute of Medical Oncology
Bern University Hospital
Bern, Switzerland
since 2006

Prof. Holger Moch, MD
Institute of Surgical Pathology
Zurich University Hospital
Zurich, Switzerland
since 2006

Prof. Simone Benhamou, PhD
Inserm Unit 946 "Variabilité génétique et maladies humaines"
French National Institute of Health and Medical Research (Inserm)
Paris, France
since 2011

Prof. Adrian Ochsenbein, MD
Institute of Medical Oncology
Bern University Hospital
Bern, Switzerland
since 2006

Prof. Maria Blettner, PhD
Institute of Medical Biostatistics, Epidemiology and Informatics (IMBEI)
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Johannes Gutenberg University Mainz
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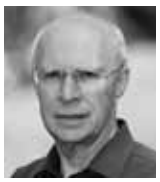
since 2010

Prof. Martin Pruschy, PhD
Department of Radiation Oncology
Zurich University Hospital
Zurich, Switzerland
since 2010

Prof. Dr. sc. nat. Ruth Chiquet Ehrismann
Friedrich Miescher Institute for Biomedial Research (FMI)
Basel, Switzerland
since 2013

Prof. Freddy Radtke, PhD
Swiss Institute for Experimental Cancer Research (ISREC)
Swiss Federal Institute of Technology Lausanne (EPFL)
Epalinges, Switzerland
since 2007



Prof. Kurt Fritzsche, MD
Department of Psychosomatic Medicine and Psychotherapy
Freiburg University Hospital
Freiburg im Breisgau, Germany
since 2009

Prof. Dr. med. Curzio Rüegg
Department of Medicine
University of Fribourg
Fribourg, Switzerland
since 2013

Prof. Silke Gillessen, MD
Oncology/Haematology Clinic
Cantonal Hospital St. Gallen
St. Gallen, Switzerland
since 2013

Prof. Beat W. Schäfer, PhD
Department of Oncology
Children's Hospital Zurich
University Children's Clinic
Zurich, Switzerland
since 2012

Prof. Primo Schär, PhD
Department of Biomedicine
University of Basel
Basel, Switzerland
since 2010

Prof. Friedrich Stiefel, MD
Liaison Psychiatry Service
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Lausanne, Switzerland
since 2007

Prof. Jürg Schwaller, MD
Department of Biomedicine
University of Basel
Basel, Switzerland
since 2013

PD Emanuele Zucca, MD
Oncology Institute of Southern Switzerland (IOSI)
Ospedale San Giovanni
Bellinzona, Switzerland
since 2013

Prof. Hans-Uwe Simon, MD, PhD
Institute of Pharmacology
University of Bern
Bern, Switzerland
since 2008

Prizes for outstanding achievements in cancer research and fighting cancer

The Swiss Cancer League (SCL) awards the Cancer Prize to recognize extraordinary contributions to cancer research and the fight against cancer. In addition, the Research Funding Department of the SCL organizes the request for proposals and the application review process for the Swiss Bridge Award. The Robert Wenner Award was not given in 2013.

Since 1960 the Swiss Cancer League has awarded the Cancer Prize of 10,000 francs. It recognizes persons who have made excellent contributions to cancer research or outstanding efforts to promote research activities in the areas of prevention, early detection, and treatment of cancer. The Cancer Prize of 2013 was awarded to *Prof. Reto Obrist, MD*, former head physician and director of the oncology department of the Canton of Valais.

Coordinated and comprehensive fight against cancer

Oncosuisse, the Swiss Cancer Organization, launched the first National Cancer Programme 2005–2010 (NCP I) in October 2005; it was developed on behalf of the Federal Office of Public Health (FOPH) and the Swiss Conference of the Cantonal Ministers of Public Health (CMPH). There were numerous obstacles to be overcome with this project, such as the federalist structures of the Swiss health care system, the discrepancy between cantonal sovereignty and federal sovereignty, the fragmented system with its many actors, and uncertain financing.

But with the NCP I, success was achieved in improving the importance of the fight against cancer on the national health agenda and optimizing cooperation among the professional associations and organizations, thus smoothing the way for a coordinated, coherent, and comprehensive fight against cancer in Switzerland. Playing a leading role here was Reto Obrist, director of Oncosuisse from 2002 to 2009, who was awarded the Cancer Prize for his outstanding contribution to the development and implementation of NCP I.

www.krebsliga.ch/krebspreis

Kurt Bodenmüller, lic. phil. nat.
Communications manager of the Scientific Office, Swiss Cancer League and Swiss Cancer Research foundation, Bern

Swiss Bridge Award 2013
Last year, the SWISS BRIDGE Foundation presented the 13th SWISS BRIDGE Award for Cancer Research with a prize of 500,000 francs. The SWISS BRIDGE Award was given in 2013 for "Health services research in oncology", and four scientists were honoured for their excellent research in that field. The focus of the four research projects was the best possible treatment and care meeting the needs of patients with cancer – in view of patients' longer-term health and quality of life and also from the point of view of health care economics.

The four researchers from Switzerland, Germany, and Italy shared the award as follows:

Prof. Christine Bouchardy, MD, head of the Geneva Cancer Registry, Institute for Social and Preventive Medicine, University of Geneva; 150,000 Swiss francs for the project: **Breast cancer quality of care and outcome according to surgeon's caseload**

Prof. Lisa Licitra, MD, chief of Head and Neck Cancer Medical Oncology Unit, IRCCS Foundation National Cancer Institute, Milan; 125,000 Swiss francs for the project: **Health and economic outcomes of two different follow-up strategies in effectively cured advanced head and neck cancer**

Heide Götze, PhD, Department of Medical Psychology and Medical Sociology, University of Leipzig; 125,000 Swiss francs for the project: **Long-term consequences of cancer and its treatment and satisfaction with health services – predictors of physical and mental health in long-term survivors**

PD Sibil Tschudin, MD, Department of Obstetrics and Gynaecology, Gynaecological Social Medicine and Psychosomatics, Basel University Hospital; 100,000 Swiss francs for the project: **Decisional conflict of young cancer patients with regard to fertility preservation – effects of an online decision-aid tool**

A total of 27 projects were submitted by researchers who are working at academic cancer research institutes in Europe. A scientific committee of nine experts in Switzerland and four other countries was responsible for the peer review process. Following the evaluation, eight applicants were invited to write individual, detailed project studies from which, ultimately, the four named winners were chosen. The Research Funding department of the SCL was responsible for the request for proposals and organization of the application review process.

The SWISS BRIDGE Foundation was founded in 1997 at the initiative of Thomas Hoepli, managing director and foundation board member, with the support of the SCL. The aim of the foundation is to financially support high-quality cancer research projects in Switzerland and other countries with the help of charitable donors and foundations. Since its founding, the SWISS BRIDGE Foundation has awarded more than 20 million francs for research work in Belgium, Brazil, Germany, England, France, Israel, Italy, Norway, Sweden, Spain, and Switzerland.

www.swissbridge.ch

National Strategy Against Cancer 2014–2017

Health services research

In July 2013 the federal government and the cantons approved the National Strategy Against Cancer 2014–2017 (NSC). The National Strategy was developed by Oncosuisse in collaboration with numerous actors and experts on behalf of the platform Dialog Nationale Gesundheitspolitik. The Swiss Cancer League (SCL) has operations responsibility for setting up and managing the implementation of the NSC. This article illustrates the complex implementation of the NSC objectives taking the example of the NSC project "health services research". And it shows how these aims are embedded in existing national strategies and measures for an important field of research that in Switzerland is still in its infancy.

As a strategic policy platform for the fight against cancer in Switzerland, Oncosuisse (the Swiss Cancer Organization) launched the second National Cancer Programme for Switzerland 2011–2015 (NCP II) in January 2011. It was developed together with the Swiss cancer organizations and with the support of the federal government and the cantons.[1] NCP II outlines 10 central fields with over 100 objectives and recommendations for improving the fight against cancer and making it more efficient. The main goals of NCP II are the following: All persons residing in Switzerland will have the same right to low cancer risk through prevention and early detection, appropriate diagnosis and treatment based on the latest findings, and psychosocial and palliative care.

The first National Strategy Against Cancer

From the start there was consensus that for policy-supported implementation of NCP II, it would be necessary to prioritize and group the objectives, taking into account the limited resources, the structures as they developed in Switzerland, and projects already ongoing in the field. Under the guidance of Oncosuisse and in a broad process involving numerous experts, organizations, and institutions, the (first) National Strategy Against Cancer 2014–2017 (NSC) was developed.[2] In July 2013 the NSC was approved by *Dialog Nationale Gesundheitspolitik*, which is the joint platform of the federal government and the cantons that commissioned the strategy.

Over the course of 2013 and based on the NSC, which is broadly anchored scientifically, medically, and politically, further prioritization work set out seven fields for action and 15 prioritized projects for the areas of *prevention, care,* and *research*. These are guided by three fundamental principles: involvement of all areas through coordination and cooperation, person-centred care through integrated care, and high quality for all through equal opportunity.

Rolf Marti, PhD
Head of the Scientific Office, Swiss Cancer League and director of the Swiss Cancer Research foundation; member of the core group "Implementation of the NSC"

Kurt Bodenmüller, lic. phil. nat.
Communications manager of the Scientific Office, Swiss Cancer League and Swiss Cancer Research foundation, Bern

Project organization and implementation

On behalf of the platform *Dialog Nationale Gesundheitspolitik*, Oncosuisse is responsible for setting up and running the complex project organization of the NSC and has delegated operational responsibility to the SCL. In a further step, the NSC core group worked hard to structure the diverse projects optimally so that the objectives of the strategy can be achieved in the most effective way possible. For this reason, projects that had many parallels and cross-connections in content and that served to reach common objectives were grouped in 10 project clusters (Figure 1).

From March to July 2014 a workshop was held for each project cluster, where the organization of the individual projects was tackled together with the organizations involved in an area and selected experts. The three main goals of the workshops were to:

1) Examine the objectives of the project and the project cluster,
2) Define the tasks necessary for achieving the objectives and set up a common rough project plan,
3) Outline the project organization and determine the project management based on the task structure.

Figure 1
Overview of the 3 areas prevention, care and research,
the 7 fields for action, the 15 projects, and the 10 project clusters of the National Strategy Against Cancer (NSC)

Fields for action	Projects	Project cluster
1. Prevention	1.1 Structural measures & health literacy	A. Prevention & health promotion
2. Screening	2.1 Colon cancer screening programmes	B. Screening programmes
	2.2 Breast cancer screening programmes	
	2.3 Panel of experts in screening questions	C. Panel of experts in screening questions
3. Clinical pathways/ quality development	3.1 Clinical pathways	D. Clinical pathways
	3.2 Guidelines and treatment guidelines	
	3.3 Tumour boards	
4. Health services	4.1 Integrated health services organization	E. Integrated health services organization
5. Education	5.1 Self-efficacy	F. Self-efficacy
	5.2 Competence building for experts	G. Education
6. Promotion of research	6.1 Health services research	H. Health services research
	6.2 Clinical and translational research	I. Clinical and translational research
7. Epidemiology/ monitoring	7.1 Federal law on cancer registration (KRG)	J. Epidemiology and monitoring
	7.2 Treatment data and data linking	
	7.3 Knowledge transfer to practice and policy	

Prevention (1/2) **Care** (3–5) **Research** (6/7)

Health services research in oncology

Three examples from the field of cancer will clarify the concrete questions and objectives of health services research.

1. Long-term survivors
Thanks to early detection, more precise diagnosis, and especially advances in treatment, the five-year survival rate for cancer is 55–60 %. At present there are close to 300,000 persons in Switzerland who will have a cancer diagnosis in their lifetime. This also means that cancer is increasingly becoming a chronic disease, which presents different and new challenges to our complex health care system. Long-term survivors make very different demands on research and society. Questions concerning the psychosocial, medical, or economic consequences of cancer treatment, for example, questions concerning rehabilitation and return to work, and so on, can only be addressed through health services research approaches. Depending on the issue under study, medical, economical, legal, and social science dispositives ("disposing knowledge") must be integrated in the study design and combined properly. In this way health services research delivers previously missing important foundations for optimal treatment and health-policy decisions.

2. Older patients with cancer
The most important risk factor for cancer is age. Approximately 60 % of all new cancer diagnoses are for persons older than 65 years of age. Less well-known is that fact that most clinical studies in oncology are conducted largely with samples that exclude precisely this age group: Only 25 % of treated patients in clinical studies are older than 65. The reason for the exclusion is mostly the high comorbidity in this age group. That means that important results – such as the results of clinical trials for approval of new cancer drugs, which often also inform treatment guidelines – are generated in studies in which the main parties affected and their particular medical situation are clearly underrepresented. Here, we must necessarily depend on health services research studies that are willing and able to analyse treatment results under everyday conditions. In a second step, the data obtained can and must be taken into consideration in the optimization of treatment guidelines.

3. Quality of life and life situation
Many clinical research efforts still centre on the goal to cure, or successfully treat, persons with cancer. Survival (without remission) is the central endpoint of most trials. However, for persons with cancer, their families, and the persons treating them, many new, previously little researched questions have moved increasingly into focus that can only be studied adequately in health services research: questions concerning quality of life, inpatient versus outpatient care, services and competencies of Spitex oncology outpatient care services, palliative care, and so on. There is a demonstrated, particularly great need for research on the specific needs of older and very elderly persons with cancer. This holds also for the service providers treating them primary care physician, oncologist, psychologist, and nursing professionals.

Project cluster "Health services research"

Within the NSC field for action "Promotion of research", one of the prioritized objectives is to build up and strengthen health services research in Switzerland. Health services research analyses the quality, effectiveness, and economic efficiency of medical services under everyday conditions (see box). On the occasion of the workshop on the project cluster "Health services research", the project aims and measures defined in the NSC were discussed and adjusted *(the changes are shown in italics)*.

1) Health services research will be established and institutionalized.
   - A research committee will be established with the participation of the professional organizations and associations to promote exchange on relevant research issues.
   - *Health services research will be institutionalized in an interdisciplinary form.*
   - *An oncology-specific module for a National Research Programme (NRP) on health services research will be submitted.*

2) Practice-oriented research questions will be taken up and studied in interdisciplinary research studies.
   - In the research work there will be a focus on research topics in public health, health economics, palliative care, and nursing.
   - Cooperation among the researchers at different universities and hospitals will be strengthened.

3) The Federal Office of Public Health (FOPH) and the Swiss Conference of Cantonal Ministers of Public Health (GDK) support health services research (including outcome data) in the framework of their jurisdictions as an independent and relevant area of research and utilize the findings in planning.

At the workshop a "health services research" working group was set up under the lead of the director of the Swiss Cancer Research foundation, and the group has since been dedicated to the implementation of the aims and measures. In view of the interdisciplinary nature of health services research and the parallels with two other research-relevant project clusters – "Epidemiology" and "Clinical and translational research" – coordination and continuous exchange among the working groups is essential. In addition, partnerships need to be formed outside of the cancer community, as the aims of the project cluster "Health services research" go beyond the field of oncology. Along with the NSC, several national initiatives are targeted at strengthening health services research in Switzerland.

Health services research in Switzerland

Although health services research in other countries such as the United States, the United Kingdom, the Netherlands, and Germany has been developed extensively for a long time, it is only in the last few years that awareness of the need for this field of research has grown in Switzerland. Health services research is not anchored in institutions, and there is no networking among the actors and no coordination of research activities. In addition, there is no comprehensive national promotion of the type of research. Therefore, in many areas of health services provision, there exist none of the scientific foundations that are indispensable for evidence-based health care policy making.

To improve health services provision and to address the main weaknesses of the Swiss health system (limited transparency, incomplete statistical and analytical basis, inefficiencies and the fact that the poor quality of certain services goes unrecognized), in January 2013 the Federal Council set out the Council's health policy priorities for the next eight

Health services research: Definitions and objectives

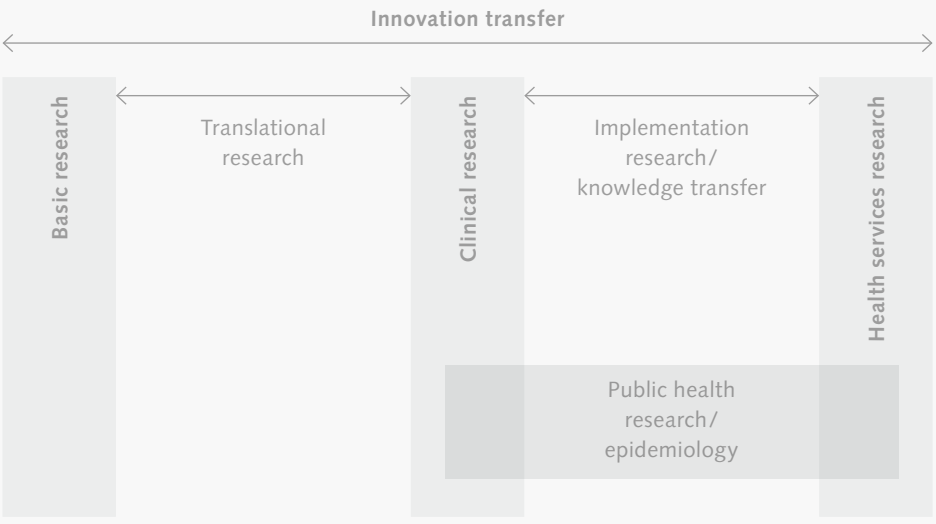
Excerpted from: "A1. Was ist Versorgungsforschung?", in: Schweizerische Akademie der Medizinischen Wissenschaften (SAMW), ed. *Stärkung der Versorgungsforschung in der Schweiz. Swiss Academies Reports 9(1)* (pp. 19-21). Basel: SAMW; 2014.[3]

«Alongside basic and clinical research, health services research has become established as a third pillar of medical research in many countries. Basic biomedical research studies biological processes and their significance for medical applications, and clinical research investigates the effectiveness of new treatments with selected patients and participants under defined study conditions. In contrast, health services research analyses the effectiveness of medical care under everyday conditions. With this, it aims to minimize the gulf between the evidence from clinical trials and actual care practice (evidence/performance gap).

Health services research studies how people gain optimal access to adequate medical care and how this care can made as efficient as possible so that it has an optimal effect on patients. The term "health services" refers not only to patients but also to the healthy population to be served (for example, in the area of prevention), and thus to patient care as well as health care.

In the United States, the *Agency for Healthcare Research and Quality* (AHRQ) defines health services research as follows: "Health services research examines how people get access to health care, how much care costs, and what happens to patients as a result of this care. The main goals of health services research are to identify the most effective ways to organize, manage, finance, and deliver high quality care; reduce medical errors; and improve patient

Figure 2
The three pillars of research in medicine and health care system
(according to Pfaff & Schrappe, 2011)[3]



Sandzeichnung, Videostill, 2012

safety".[4] This definition by the AHRQ puts the core areas of health services research in a nutshell – namely, access, appropriateness, and the costs of care – and makes it clear that health services research is patient-centred and focused on outcome quality.

The definition of health services research most widely disseminated in German-speaking countries derives from Pfaff et al.[5] Pfaff sees the "last mile" of the health system – that is, looking at patient care under the real life conditions of routine provision of medical services to the public as the central focus of health services research. Offering a methodological/functional definition, Pfaff describes health services research as an "interdisciplinary field of research which gives an account, and causal explanations, of health services and the framework within which they are delivered; promotes the development of scientifically based health service concepts; monitors the implementation of new health service concepts; and evaluates the effectiveness of health service structures and processes under everyday conditions"[5] (Figure 2).

The goal of multi- and transdisciplinary health services research is to generate evidence-based information on how to optimize the structures of patient and health care, increase the quality and efficiency of health services, reduce underprovision and overprovision, and increase patient-centredness and patient safety. Thus, the findings of health services research benefit not only patients and service providers but also policy- and decision-makers in government and the economy.»

years in the "Health2020" report.[6] Among other things, the report calls explicitly for the establishment and strengthening of health services research in Switzerland. A report issued in 2012 by the Swiss Conference of Cantonal Ministers of Public Health (GDK) and the FOPH on new models for the delivery of primary care[7] also places a priority on expanding and strengthening health services research in Switzerland, as does also the Federal Council's Master Plan of 2013,[8] *Massnahmen des Bundes zur Stärkung der biomedizinischen Forschung und Technologie* (government measures to strengthen biomedical research and technology).

Pioneering work by the SAMS

The Swiss Academy of Medical Sciences (SAMS) is playing a pioneering role. Together with the Gottfried & Julia Bangerter-Rhyner-Stiftung, SAMS launched a new funding programme in health services research in 2012 to establish and develop this area of research in Switzerland. To this purpose the Bangerter-Rhyner-Stiftung is providing one million Swiss francs in funding for pilot projects, research studies, and scholarships/grants.

For three years now, SAMS – with support from the Bangerter-Rhyner-Stiftung and in cooperation with different partners – has organized an annual national symposium on health services research. The purpose is transfer of knowledge, presentation of up-to-date research findings, awarding of prizes for outstanding research, and interdisciplinary exchange. It also serves the building of a health services research community, made up of representatives of the different special areas and professions. The first symposium in 2012, which was conducted with the active participation of the Swiss Group for Clinical Cancer Research (SAKK), the Swiss Cancer Research foundation, and the SCL, was dedicated to health services research in oncology.

SAMS, as the lead organization and with the involvement of various actors including also the Swiss Cancer Research foundation and the SCL, was requested by the Federal Office of Public Health (FOPH) to prepare a paper on strengthening health services research in Switzerland.[3] The paper was written in the framework of the Federal Council's Primary Care Master Plan and published in March 2014. The paper essentially provides answers to the question as to what kind of health services research is needed in Switzerland. The report also offers recommendations for the medium- and long-term building of research expertise, infrastructures, database, promotion of young researchers, and funding sources in the area of health services research.

National Research Programme

Based on the SAMS paper and led by Prof. Thomas Rosemann, MD, PhD, head of the Institute of Primary Care and Health Services Research at University Hospital Zurich, SAMS submitted a proposal for a National Research Programme (NRP) on health services research in Switzerland in January 2014.[9] With this, the first aim of the NSC for the project "Health services research" was achieved.

The NRP on health services research is intended to make possible research on urgent issues, such as overprovision, underprovision, inappropriate care in the Swiss health care system, optimal resource allocation (interprofessional cooperation) in medical care, access and provision to vulnerable patients in the health care system, and care of patients with chronic diseases and multimorbidity. The NRP also provides Switzerland with an opportunity to catch up in the field of health services research.

A total of 69 proposals for new NRPs were submitted to the State Secretariat for Education, Research and Innovation (SERI); the Swiss National Science Foundation (SNSF) will conduct a feasibility study for six of these research topics, including health services research. The Federal Council is expected to determine the topics and the budgets of the new NRPs in the spring of 2015 and commission the SNSF to conduct the programmes. As there is broad support and a demonstrated need for the research, the chances for approval of an NRP on health services research are good. And that brings another aim of the NSC – a cancer-specific health services research module – within reach.

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9. www.sbfi.admin.ch/nfp

Research funding by the cantonal and regional cancer leagues

The cancer league is organized as an association made up of 19 cantonal and regional cancer leagues as well as the umbrella organization, the Swiss Cancer League. In 2013, eight cantonal cancer leagues – including the Geneva Cancer League – gave a total of 3.1 million francs to cancer research projects and institutes. Providing funding of approximately one million francs per year, the Geneva Cancer League is the cantonal cancer league that invests the most money in cancer research.

The Geneva Cancer League funds research projects at Geneva University Hospital (HUG) and at the Faculty of Medicine and Faculty of Sciences at the University of Geneva with the aim to contribute towards increasing the effectiveness of cancer treatments in the short and long term. The Geneva Cancer League has supported cancer research benefitting persons with cancer since its founding in 1924. The first research project supported was a project on treating cervical cancer at the Institute of Radiation Therapy. Funding research is one of the main aims set out in the statutes of the Geneva Cancer League.

The budget of the Geneva Cancer League is discussed and approved at the annual general assembly at the request of the board of directors. At a special session headed by the author of this article, the board decides on the allocation of the funds based on detailed information on the individual research projects. In the past five years, approximately one-third of the available monies of 3 to 3.6 million francs went to support research projects. This prioritization accords with numerous charitable donors' wish that their donations be used for cancer research activities. Research funding is next largest budget position after help for persons with cancer.

Funding of projects in different areas of research

The Geneva Cancer League funds a broad range of research projects:

– Clinical research, with the exception of large clinical trials, the costs of which exceed the funds of the Geneva Cancer League. But the Geneva Cancer League supports the conducting of clinical pilot studies, such as a pilot study initiated by Prof. Pierre-Yves Dietrich, director of the Centre of Oncology at Geneva University Hospital, for which he was awarded the distinguished Cancer Researcher of the Year Award by the Gateway for Cancer Research. This innovative study is on immunotherapy for glioblastoma. Another example is adjuvant treatment of melanoma using beta-blockers; the initial results obtained thanks to the support of the Geneva Cancer League served as the basis for the conducting of an international study.
– Applied research on common types of cancer that affect a large part of the population (such as breast cancer), on types of cancer that are hard to detect in early stages (such as ovarian cancer), and on types of cancer that are difficult to treat (such as brain tumours, pancreatic cancer, and liver cancer).

Prof. Luc Perrin, MD, Dr h.c.
Member of the board of the Geneva Cancer League, honorary professor of virology at Geneva University Hospital (HUG), Geneva

– Research on new diagnostic instruments, such as for leukaemias or for better assessment of the prognosis of patients with breast cancer, and on the advisability of adjuvant chemotherapy with certain types of cancer.
– Basic research to find new ways and targets for cancer treatment – a long-term perspective with great potential.
– Funding for prevention and screening activities.
– Funding for new services for research not yet financed by HUG. At present, for example, we are supporting the Centre for Oncology, which is participating in a programme on genetic characterization of selected types of cancer.

Submission, review, and monitoring of research projects

Grant applications for new research projects can be submitted to the Geneva Cancer League up to 1 October of the current year. Applications are submitted using standard forms that are similar to the forms used by the Swiss National Science Foundation (SNSF). The applications are reviewed by the person responsible for research, currently the author of this article, and the president of the Geneva Cancer League, Prof. Bernard Chapuis, who consult the applicants and, if needed, obtain the opinions of external experts. Approximately 30 % to 50 % of the grant applications are submitted by women. These grant applications receive priority support in order to promote gender balance among future academic researchers. The two reviewers exchange their opinions and prepare a report on each grant application that includes recommendations. The reports are forwarded to the manager of and to the board of the Geneva Cancer League, which – after discussion with the two reviewers – makes the final funding decisions. The results of the review are then communicated to the grant applicants.

About one-half of the grant applications submitted can be supported. For a research project to receive funding, the following three conditions must be fulfilled:
– In publications emerging out of research that is funded fully or in part by the Geneva Cancer League, the funding by the Geneva Cancer League must be mentioned in the acknowledgements.
– The Geneva Cancer League must receive an annual and/or final report, with enclosure of a copy of the supported publications. For research projects with a duration of several years, the research report serves as the basis for the League's decision on continuing funding of the project.
– Each year, a financial report on the use of the granted funds must be prepared. For grants to university research groups, the report must be prepared by the financial services of the department that is responsible for the administration of university funds.

Prof. Luc Perrin, MD, Dr h.c.
Luc Perrin is honorary professor of virology at HUG. Perrin set up the Laboratory of Virology there and frequently publishes papers on clinical virology in the areas of HIV, hepatitis, and influenza. He has been a member of the board of the Geneva Cancer League for many years and is responsible for the review of research grant applications.

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www.lgc.ch/fr/recherche

List of supported funded research projects and institutions in 2013

The list shows the financial contributions granted in 2013.

Basel Cancer League

Christofori Gerhard | CHF 55,000.–
Institut für Biochemie und Genetik, Universität Basel, Basel
High-content identification and modulation of signalling pathways underlying epithelial-mesenchymal transition (EMT) and cancer metastasis

Heinzelmann-Schwarz Viola | CHF 30,000.–
Klinik für Operative Gynäkologie und Gynäkologische Onkologie, Universitätsspital Basel, Basel
The human N-acetylglucosaminyltransferase MGAT3 as a potential specific biomarker in ovarian cancer

Hohmann Joachim | CHF 5,000.–
Klinik für Radiologie und Nuklearmedizin, Universitätsspital Basel, Basel
Comparison of ^{18}F-FDG-PET/CT and ultrasonography (abdomen and peripheral lymph nodes) in the initial staging and the follow-up of patients with melanoma

Hynes Nancy | CHF 30,000.–
Friedrich Miescher Institut für biomedizinische Forschung (FMI), Basel
Aberrant Ret expression causes mammary tumours and developmental defects during the post-lactational transition

Kovac Michal | CHF 45,000.–
Institut für Pathologie, Universitätsspital Basel, Basel
Deep exome sequencing approach to investigate the evolution of multi-focal hepatocellular carcinoma through space and time

Müller Philipp | CHF 25,000.–
Departement Biomedizin, Universitätsspital Basel, Basel
Exploring the immunomodulatory mechanisms of the tyrosine kinase inhibiter axitinib in tumour-bearing hosts: implications for combination therapies with anti-cancer immunotherapy

Obermann Ellen | CHF 6,000.–
Institut für Pathologie, Universitätsspital Basel, Basel
Evaluation of the mechanical properties of metastatic tumour cells of the breast by atomic force microscope (AFM)

Rothschild Sacha | CHF 20,000.–
Klinik für Onkologie, Universitätsspital Basel, Basel
Methylphenidate for the treatment of cancer-related fatigue

Ruiz Christian | CHF 20,000.–
Institut für Pathologie, Universitätsspital Basel, Basel
Evaluation of the role of ANO1 as a potential therapeutic target in urinary bladder cancer

Spagnoli Giulio | CHF 64,000.–
Departement Biomedizin, Universitätsspital Basel, Basel
Expansion and functional analysis of "bulk"- and tumour-associated antigen specific stem cell memory CD8$^+$ T-cells from peripheral blood of healthy donors and patients with melanoma or non-small cell lung carcinoma

Bern Cancer League

Bouchet Audrey | CHF 60,000.–
Institut für Anatomie, Universität Bern, Bern
Increased vascular permeability by synchrotron microbeam radiation generates a highly efficient drug delivery system for tumour treatment

Dufour Jean-François | CHF 20,000.–
Departement Klinische Forschung, Universität Bern, Bern
The Bern hepatocellular carcinoma (HCC) cohort

Höpner Sabine | CHF 40,000.–
Departement Klinische Forschung, Universität Bern, Bern
Lymphotoxin-β receptor (LTBR) signalling in leukaemic stem cells

Marti Thomas | CHF 60,000.–
Departement Klinische Forschung, Universität Bern, Bern
Targeting tumour-initiating cells in lung cancer

Müller Loretta | CHF 43,000.–
Departement Klinische Forschung, Universität Bern, Bern
Carcinogenic potential of gasoline car exhaust (including nanoparticles) and their effect on natural killer cells

Peng Ren-Wang | CHF 70,000.–
Departement Klinische Forschung, Universität Bern, Bern
Functional identification and molecular targeting of human lung cancer stem cells

Schäfer Stephan | CHF 70,000.–
Institut für Pathologie, Universität Bern, Bern
Molecular characterization of adenosquamous carcinoma of the lung as a prime type model of tumour heterogeneity

Schlapbach Christoph | CHF 50,000.–
Universitätsklinik für Dermatologie, Inselspital, Universitätsspital Bern, Bern
Characterizing human interleukin 9-producing T-helper memory cells and their role in anti-tumour immune response in malignant melanoma

Schucht Philippe | CHF 25,000.–
Universitätsklinik für Neurochirurgie, Inselspital, Universitätsspital Bern, Bern
Extent of resection thresholds as predictor of survival in patients with glioblastoma

Central Switzerland Cancer League

Diebold Joachim | CHF 50,000.–
Zentralschweizer Krebsregister, Luzerner Kantonsspital, Luzern
Do the new possibilities for targeted therapy lead to an improvement in survival rates of advanced lung cancer patients in Central Switzerland?

Eastern Switzerland Cancer League

Ludewig Burkhard | CHF 100,000.–
Institut für Immunbiologie, Kantonsspital St. Gallen, St. Gallen
Systems biology approach to molecularly characterize the lung cancer microenvironment

Ansari Marc | CHF 50,500.–
Département de pédiatrie, Hôpitaux universitaires de Genève (HUG), Genève
Association of a CTH gene variant with veno-occlusive disease in children receiving busulfan before haematopoietic stem cell transplantation

Cohen Marie | CHF 99,168.–
Département de gynécologie et d'obstétrique, Hôpitaux universitaires de Genève (HUG), Genève
Novel therapeutic approaches against ovarian cancer recurrence

Curran Joseph | CHF 106,909.–
Département de microbiologie et médecine moléculaire, Université de Genève, Genève
The 5'UTR fingerprint: a new diagnostic marker for breast cancer

Dietrich Pierre-Yves | CHF 140,000.–
Service d'oncologie, Département de médecine interne, Hôpitaux universitaires de Genève (HUG), Genève
Identification and validation of glioma antigen: towards immunotherapies for brain tumours

Irminger Irmgard | CHF 50,000.–
Département de gynécologie et d'obstétrique, Hôpitaux universitaires de Genève (HUG), Genève
Regulation of the oncogenic isoforms of the tumour suppressor BARD1 in cancer by microRNAs and non-coding RNAs

Le Gal Frédérique | CHF 30,000.–
Département des spécialités de médecine, Service de dermatologie et vénérologie, Hôpitaux universitaires de Genève (HUG), Genève
Skin cancer screening using high-sensitivity infrared imaging

Le Gal Frédérique | CHF 120,000.–
Département des spécialités de médecine, Service de dermatologie et vénérologie, Hôpitaux universitaires de Genève (HUG), Genève
Beta-blockers in the adjuvant treatment of melanoma, an interventional clinical study

Mandriota Stefano | CHF 100,230.–
Département de pédiatrie, Division d'onco-hématologie, Hôpitaux universitaires de Genève (HUG), Genève
The ATM/p53 signalling pathway in the regulation of cellular senescence

Martinou Jean-Claude | CHF 96,000.–
Département de biologie cellulaire, Faculté des sciences, Université de Genève, Genève
Role of the mitochondrial pyruvate carrier in the proliferation and metastasis of breast cancer cells

Preynat-Seauve Olivier | CHF 99,986.–
Laboratoire d'immuno-hématologie transfusionnelle, Hôpitaux universitaires de Genève (HUG), Genève
Identification of miRNA targets for glioblastoma using a novel in vitro model

Reith Walter | CHF 111,159.–
Département de pathologie et d'immunologie, Faculté de médecine, Université de Genève, Genève
Identifying the cellular functions and regulatory networks that underlie the link between microRNA-155 and cancer

Thore Stéphane | CHF 90,000.–
Département de biologie moléculaire, Faculté des sciences, Université de Genève, Genève
Steroid receptor RNA activator: a new target for modulating the hormonal response in cancer cells

Tille Jean-Christophe | CHF 70,000.–
Département de pathologie clinique, Faculté de médecine, Université de Genève, Genève
Role of heparan sulfate in endometrioid carcinoma: tissue remodelling, angiogenesis and lymphangiogenesis

Wehrle-Haller Bernard | CHF 70,500.–
Département de physiologie cellulaire et métabolisme, Centre médical universitaire (CMU), Genève
Kinase-independent functions of the receptor tyrosine kinase c-kit in the persistence and adhesion of cancer stem cells to their environmental niche

Sandzeichnung, Videostill, 2012

Thurgau Cancer League

Fleischmann Achim | CHF 53,714.–
Pathologie, Kantonsspital Münsterlingen, Münsterlingen
Promotion of cancer research, focused on the area of gynaecological and urological tumours

Legler Daniel | CHF 33,333.–
Biotechnologie Institut Thurgau, Universität Konstanz, Kreuzlingen
Breast cancer project

Reuter Christiane | CHF 25,000.–
Radioonkologie, Kantonsspital Münsterlingen, Münsterlingen
Study of intraoperative radiotherapy of the breast

Ticino Cancer League (Fondazione ticinese per la ricerca sul cancro)

Catapano Carlo | CHF 100,000.–
Istituto oncologico della Svizzera italiana (IOSI), Bellinzona
Non-coding RNAs and epigenetic networks in prostate cancer pathogenesis and novel therapeutic strategies

Ceppi Francesco | CHF 18,000.–
Hôpital Notre-Dame, Montréal, Canada
Post-graduate training in paediatric oncology

Civenni Gianluca | CHF 50,000.–
Istituto oncologico della Svizzera italiana (IOSI), Bellinzona
Isolation of stem cells from human prostate biopsy to study tumour initiation

Frattini Milo | CHF 50,000.–
Istituto cantonale di patologia, Locarno
Investigation of the role of NEU3 in colorectal carcinogenesis

Molinari Francesca | CHF 50,000.–
Istituto cantonale di patologia, Locarno
Identification of new alterations in the small intestine adenocarcinoma through new sequencing methodology

Zurich Cancer League

Bernasconi Michele | CHF 72,045.–
Experimentelle Infektiologie und Krebsforschung, Kinderspital Zürich, Universitäts-Kinderkliniken, Zürich
Role of proprotein convertases in paediatric sarcomas: useful theragnostic targets?

Bornhauser Beat | CHF 67,045.–
Forschungsgruppe Leukämie/Onkologie, Kinderspital Zürich, Universitäts-Kinderkliniken, Zürich
Large scale drug response profiling to identify new targets in refractory leukaemia

Graf Rolf | CHF 69,720.–
Klinik für Viszeral- und Transplantationschirurgie, Universitätsspital Zürich, Zürich
Inflammation contributes to the regression of acinar-to-ductal metaplasia in the injured pancreas

Hottiger Michael | CHF 70,625.–
Institut für Veterinärbiochemie und Molekularbiologie, Universität Zürich, Zürich
Assessment of ADP-ribosylomes to identify specifically ADP ribosylated proteins that regulate PARP inhibitor sensitivity of cancer cells

Müller Anne | CHF 84,220.–
Institut für Molekulare Krebsforschung, Universität Zürich, Zürich
Epigenetic silencing of tumour suppressor genes in the pathogenesis of diffuse large B-cell lymphoma

Münz Christian | CHF 58,116.–
Institut für Experimentelle Immunologie, Universität Zürich, Zürich
Boosting of NY-ESO-1-specific re-directed T-cells

Nadal David | CHF 78,061.–
Abteilung Infektiologie und Spitalhygiene, Kinderspital Zürich, Universitäts-Kinderkliniken, Zürich
Natural killer cell control of Epstein-Barr virus-induced cancerous B-cell transformation

Rohrer Bley Carla | CHF 51,115.–
Abteilung für Radio-Onkologie, Universität Zürich, Zürich
In vivo profiling of DNA damage and repair kinetics after anti-neoplastic treatment: use of a minimally invasive approach

Tabatabai Ghazaleh | CHF 51,300.–
Klinik für Neurologie, Universitätsspital Zürich, Zürich
Thymosin beta-4 in malignant gliomas: a novel regulator of angiogenesis?

Weber Achim | CHF 40,000.–
Institut für Klinische Pathologie, Universitätsspital Zürich, Zürich
Role of innate lymphoid cells (ILC) in intestinal inflammation and carcinogenesis

Basel Cancer League

Christofori Gerhard | **High-content identification and modulation of signalling pathways underlying epithelial-mesenchymal transition (EMT) and cancer metastasis**
Institut für Biochemie und Genetik, Universität Basel, Basel
Duration: 01. 09. 2013 – 01. 03. 2015

Most cancer deaths are due to the systemic dissemination of cancer cells and the formation of secondary tumours (metastasis) in distant organs. Obviously, the migratory and invasive capabilities of cancer cells are critical parameters in the metastatic cascade. 90 % of all cancers originate from epithelial tissues and to leave the primary tumour and to invade into the surrounding tissue tumour cells dissolve their cell-cell contacts and adjust their cell-matrix adhesion sites to a more transient, migratory and invasive mode. Such temporary and reversible phenomenon is known as epithelial-to-mesenchymal transition (EMT), a multi-stage process that involves distinct genetic and epigenetic alterations and leads to metastasizing, tumour-seeding cells with stem cell-like capabilities, potentially cancer stem cells.

Employing various cellular models of EMT *in vitro* and mouse models of cancer *in vivo*, we take a focussed approach to identify the signalling pathways and their specific kinase and phosphatase components that functionally contribute to EMT and malignant tumour progression. Subsequently, we modulate the function of these signalling pathways in order to prevent EMT or to differentiate cancer cells into non-malignant, differentiated tumour cells. The experiments aim at the identification of molecular targets for the design and development of novel cancer therapies.

Heinzelmann-Schwarz Viola | **The human N-acetylglucosaminyltransferase MGAT3 as a potential specific biomarker in ovarian cancer**
Klinik für Operative Gynäkologie und Gynäkologische Onkologie, Universitätsspital Basel, Basel
Duration: 01. 08. 2013 – 31. 12 .2013

Advanced epithelial ovarian cancer has a poor survival rate (30 %) but prognosis improves if the cancer is diagnosed early. However, early diagnosis is often limited due to the lack of reliable and sensitive biomarkers. Identification of novel biomarkers for early detection of ovarian cancer is of immense interest. In an effort to search for ovarian cancer-specific cell surface markers we previously detected a unique glycan (carbohydrate) structure on ovarian cancer cells, which was not detectable on normal ovarian surface epithelial (HOSE) cells. This unique structure comprises a bisecting monosaccharide (GlcNAc) which correlates with the expression of MGAT3 (a glycosyltransferase) gene, proposing bisecting GlcNac as a potential ovarian cancer biomarker. As MGAT3 appears to be repressed by DNA methylation in normal HOSE but demethylated in ovarian cancer cells, we investigated the molecular mechanism of this putative epigenetic regulation of MGAT3.

Our results show that reduced DNA methylation at unique sites of the MGAT3 promoter correlates with increased expression of MGAT3 in ovarian cancer cells and that MGAT3 and bisecting GlcNAc are re-expressed in HOSE cells by the DNA methyltransferase-inhibitor 5-Aza. We propose that increased MGAT3 expression in ovarian cancer cells is regulated by DNA demethylation. Preliminary results suggest a similar mechanism for elevated MGAT3 expression in stem cell-like pools of HOSE cells from which ovarian cancer may develop.

Hohmann Joachim | **Comparison of ^{18}F-FDG-PET/CT and ultrasonography (abdomen and peripheral lymph nodes) in the initial staging and the follow-up of patients with melanoma**
Klinik für Radiologie und Nuklearmedizin, Universitätsspital Basel, Basel
Duration: 01. 12. 2013 – 30. 11. 2014

The therapeutic options for patients with melanoma depend strongly on the results of the staging examinations regarding especially lymph nodes and filiae in other organs like the liver or the lung. The detection or exclusion of such manifestations of the primary tumour is the main task for the imaging modalities of radiology and nuclear medicine. Which modality is giving the best results is subject of controversial discussions. It might either be PET/CT or ultrasonography or a combination of both. However, there are several publications for both methods but there is a lack of studies comparing both modalities in the same patients.

At the University Hospital Basel patients with melanoma are usually getting both examinations for several years. Therefore the aim of our study is to close the gap in the literature with the retrospective evaluation of the performed PET/CT and ultrasonography examinations in these patients. The benefit of the study will be to find out the optimal examination strategy for the individual patient and furthermore a possible cost reduction for the health system.

Hynes Nancy | **Aberrant Ret expression causes mammary tumours and developmental defects during the post-lactational transition**
Friedrich Miescher Institut für biomedizinische Forschung (FMI), Basel
Duration: 01. 07. 2014 – 01. 11. 2014

The receptor tyrosine kinase (RTK) Ret, a key oncoprotein in thyroid carcinoma, has also been implicated in other types of cancers. Recently, Ret copy number gains and mutations have been reported at low frequencies in breast tumours. Furthermore, we and others have reported that Ret is overexpressed in about 40 % of human tumours and this correlates with poor patient prognosis. Using a transgenic mouse model with the MMTV promoter controlling Ret expression in the doxycycline-inducible system, we show that overexpression of Ret in the mammary epithelium produces hyperplasia and mammary tumours display-

ing a solid morphology that recapitulates features of human solid ductal carcinoma *in situ*. Moreover, Ret-induced tumours express ErbB2 and are oestrogen receptor positive. Importantly Ret-induced tumours rapidly regress after doxycycline withdrawal indicating that Ret is the driving oncoprotein.

It is well known that RTKs, which are implicated in breast cancer, e. g. the ErbB receptors, also have roles in normal development. We found that Ret is highly expressed in mid-lactation. Indeed, Ret appears to have a role in the post-lactation transition to involution since when Ret is induced early in lactation we observe enhanced kinetics of involution. The involution period is well known to drive cancer progression. Thus, our results suggest that if Ret expression is deregulated during the lactation-involution transition this might contribute to breast cancer development.

Kovac Michal | **Deep exome sequencing approach to investigate the evolution of multi-focal hepatocellular carcinoma through space and time**
Institut für Pathologie, Universitätsspital Basel, Basel
Duration: 01. 09. 2013 – 01. 09. 2014

The medical strategies targeting hepatocellular carcinoma (HCC) are often hindered by tumour recurrence that may be as high as 75 % in a 5-year period. A partial explanation of this dismal figure is due to the simultaneous existence of various cancer cell types, or cancer clones, within the same tumour with different mutations in genes and molecular pathways of which only few are targetable. As more drugs targeting different members in same signalling pathway are likely to come into market in the years to come, it becomes crucial for a physician to have a clear understanding of the clonal complexity of the patient's tumour to decide, which combination of drugs should be used to achieve the longest disease-free survival. Understanding of clonal structure of multi-focal HCC tumours thus poses another challenge to be met, which has now become possible using deep next generation sequencing followed by mathematical modelling of the data.

The proposed project will provide a deeper understanding of the complexity of multi-focal HCC with the specific aim to establish the influence of tumour microenvironment and clonal structure on patient's survival. This is important clinically, as it will provide knowledge that will assist in the introduction of the personalized medicine approach to cancer, as in a heterogeneous tumour the major clone may not be the one that gives rise to recurrent, metastatic, or therapy-resistant tumour cells.

Müller Philipp | **Exploring the immunomodulatory mechanisms of the tyrosine kinase inhibiter axitinib in tumour-bearing hosts: implications for combination therapies with anti-cancer immunotherapy**
Departement Biomedizin, Universitätsspital Basel, Basel
Duration: 01. 07. 2013 – 30. 06. 2014

Recent experimental work provides strong evidence that anti-angiogenic therapies can normalize the tumour vasculature, thereby enhancing the efficacy of anti-cancer immunotherapies such as immune checkpoint-directed, therapeutic antibodies. Tumour resident c-kit positive mast cells have been shown to promote tumour angiogenesis. They can also increase the number of immunosuppressive myeloid derived suppressor cells and regulatory T-cells at the tumour site. The second-generation vascular endothelial growth factor receptor (VEGFR) inhibitor axitinib, which inhibits tumour angiogenesis by blocking VEGFRs, also interferes with c-kit signalling. Therefore axitinib may offer the benefit of a two-pillar treatment approach targeting tumour angiogenesis and c-kit dependent mast cells at the same time. Using advanced *in vivo* as well as *in vitro* tumour models we will provide an accurate immunological definition of the therapeutic relevance of this two-pillar approach as well as elucidate the immunological basis of synergies between axitinib and immune checkpoint-directed, therapeutic antibodies. Our work will provide a rational for the design of early clinical trials assessing these combination therapies in cancer patients.

Obermann Ellen | **Evaluation of the mechanical properties of metastatic tumour cells of the breast by atomic force microscope (AFM)**
Institut für Pathologie, Universitätsspital Basel, Basel
Duration: 01. 09. 2014 – 31. 08. 2015

Breast cancer is the most frequent malignancy in women in Switzerland. Tumours are nowadays often detected at an early stage and can often be cured. However, the chances of a complete cure drop significantly if metastases develop. Therefore it is important to understand, when and why a tumour metastasizes. Nanomechanical characteristics play an important role in the development of metastases. Nanomechanical properties of cells are for example the "stiffness" of single tumour cells. This stiffness can be assessed by using atomic force microscopes. We were able to show in a pilot study utilizing a special type of atomic force microscope (ARTIDIS®) that breast cancer cells in transgenic mice were significantly softer than normal breast tissue. The current study helps to establish the ARTIDIS®-technology for the use in human samples. We systematically analyse breast cancer and normal tissue for their nanomechanical properties. Our aim is to understand mechanisms of metastatic disease, predict precisely the likelihood of a tumour to seed metastases, and define potential novel therapeutic targets.

Rothschild Sacha | **Methylphenidate for the treatment of cancer-related fatigue**
Klinik für Onkologie, Universitätsspital Basel, Basel
Duration: 01.01.2014 – 31.12.2020

Cancer-related fatigue (CRF) is a subjective symptom experienced by patients at all stages of disease and increasing with advanced disease. For cancer patients fatigue is one of the most important and distressing symptoms and is clearly correlated to overall patient satisfaction and quality of life. Overall, 50–90 % of cancer patients experience fatigue. Treatment interventions for CRF may be categorized as non-pharmacologic and pharmacologic. Non-pharmacologic interventions include psychosocial interventions, exercise, dietary management and sleep therapy. The classes of drugs that have been studied most in managing CRF include stimulants (methylphenidate, modafinil), antidepressants, corticosteroids and others. Clinical data from these studies are conflicting. Therefore, there is no accepted standard therapy for CRF. The aim of this placebo-controlled trial of methylphenidate is to evaluate its efficacy for alleviating cancer-related and therapy-associated fatigue in patients with advanced/metastatic adenocarcinoma of the lung undergoing maintenance therapy with pemetrexed after platinum-based first-line chemotherapy (cohort 1) or in patients with metastatic renal cell carcinoma undergoing first-line targeted therapy with pazopanib (cohort 2).

Ruiz Christian | **Evaluation of the role of ANO1 as a potential therapeutic target in urinary bladder cancer**
Institut für Pathologie, Universitätsspital Basel, Basel
Duration: 01.10.2013 – 30.09.2014

Urothelial bladder cancer is the most common type of cancer of the urinary tract in industrialized countries. In contrast to other tumour types, such as lung or breast cancer, patients with urinary bladder cancer cannot profit from a new generation of drug therapies, called targeted therapeutics. The aim of this study is to determine if the gene ANO1 may serve as a target of such a therapy. Importantly, the gene ANO1 is located in a genomic region, which is amplified in up to 11 % of the bladder carcinomas. It has been shown that the gene ANO1 is involved in migration, a process that contributes to metastasis. In this study, we aim at analysing the expression of this gene in a larger cohort of bladder cancers and its potential clinical significance. We will analyse primary tumours, as well as lymph node and distant metastases from patients with bladder cancer. Further, we will also perform experiments with commercially available bladder cancer cell lines in order to define if the inactivation of the gene ANO1 in culture leads to a reduction in migration and in cell growth. These experiments are one of the first steps to discover, if the gene ANO1 may be suited as a target for specific therapies, at least for ANO1 positive bladder cancer patients.

Spagnoli Giulio | **Expansion and functional analysis of "bulk"- and tumour-associated antigen specific stem cell memory CD8⁺ T-cells from peripheral blood of healthy donors and patients with melanoma or non-small cell lung carcinoma**
Duration: 01.06.2013 – 31.05.2014

Experimental immunology studies have investigated the nature of T-cells best promoting the rejection of established cancers and/or the prevention of recurrences. Unexpectedly, lymphocytes killing tumour cells have proven remarkably ineffective in this regard, largely due to their inability to expand *in vivo* following interaction with target cells and short life span. In contrast, memory T-lymphocytes devoid of cytotoxic capacity and characterized by the ability to vigorously proliferate and produce cytokines in response to antigen stimulation has been shown to mediate rejection of established experimental tumours. In our studies we are addressing the identification of such lymphocytes specifically recognizing human tumour associated antigens and the development of *in vitro* protocols promoting their expansion in healthy donors and patients with cancer. A successful implementation of this project might set the stage for basic immunology investigations and for clinical immunotherapy studies based on the use of own memory T-cells in patients with cancer.

Bern Cancer League

Bouchet Audrey | **Increased vascular permeability by synchrotron microbeam radiation generates a highly efficient drug delivery system for tumour treatment**
Institut für Anatomie, Universität Bern, Bern
Duration: 01.01.2014 – 31.12.2016

Despite recent improvements, glioblastoma multiforme is still the most common and most devastating brain tumour. As the specific anatomic characteristics of solid tumours in the brain as well as the presence of a biological barrier (the blood-brain barrier) generally blocks the access of chemotherapeutic agents to all tumour cells, the efficiency of blood-borne chemotherapies is limited. Microbeam radiation therapy (MRT) is a novel radiotherapy based on micro-fractionation of X-ray beams delivered through thin beams separated by few hundred microns. Our recent observations indicate that at low dose, the MRT dramatically increased the vascular permeability without destroying the vessel integrity in a time interval beginning few minutes after MRT, a time span that we termed "therapeutic window".

The experimental use of the therapeutic window proved to be highly effective: indeed a combined treatment, MRT followed by chemotherapy, dramatically reduced the progression of glioblastoma in a mouse model; some of the tumours even disappearing. The best explanation for these positive results lies in the disruption of the barrier leading to penetration of the chemotherapeutic agents into the tumour. Based on the promising preliminary data, we intend to establish a novel treatment protocol based on the "therapeutic window" which should overcome the biological barrier and be more efficient.

Dufour Jean-François | **The Bern hepatocellular carcinoma (HCC) cohort**
Departement Klinische Forschung, Universität Bern, Bern
Duration: 01. 08. 2013 – 31. 07. 2016

Worldwide hepatocellular carcinoma is the 5th most common solid tumour. In terms of mortality from solid tumour it is number 3 worldwide. In Europe, every 11 minutes a person dies from hepatocellular carcinoma. Early diagnosis dictates the prognosis: when symptoms lead to the diagnosis, patients survive only a few months. However, when the diagnosis is made early, meaning when the tumour is small, patients can be cured. About 80 % of hepatocellular carcinoma arise in the context of cirrhosis whatever the underlying cause. Therefore, patients with cirrhosis are at risk. These patients should be screened regularly. Despite these facts, hepatocellular carcinoma is often overlooked and many patients are diagnosed too late.

This project aims at gathering epidemiological and clinical data on every patient with hepatocellular carcinoma seen at the University Hospital in Bern, who accepts to participate. Practically, patients provide specific information, including blood and urine samples, and answer questionnaire on the quality of life. This will provide for the first time in Switzerland a precise information regarding stage at diagnosis, quality of life, treatments and survival of patients with this type of cancer. This information is essential to understand the barriers to early diagnosis and to improve the management of patients with hepatocellular carcinoma.

Höpner Sabine | **Lymphotoxin-β receptor (LTBR) signalling in leukaemic stem cells**
Departement Klinische Forschung, Universität Bern, Bern
Duration: 01.10.2013 – 01.10. 2015

This project aims at investigating leukaemic stem cells and at studying the way they divide and fight off the immune response. It has been shown that the tumour necrosis factor (TNF) receptors and their ligands play a crucial role. TNF receptor form a large network, which affects the proliferation, the survival and the programmed death, called apoptosis. Using a leukaemic mouse model, we were able to study one selected TNF receptor at a time. We could show for the first time that leukaemic stem cells (LSC) in the bone marrow express the TNF receptor LTBR (Lymphotoxin β-receptor). LTBR could play a role as a new therapeutic target, as there are LTBR signalling pathways promoting the progression of chronic myeloid leukaemia as well as signalling pathways supporting cells of the immune system against cancer cells. With this project, we want to investigate further whether the LTBR signalling pathway could be a relevant therapeutic target.

Marti Thomas | **Targeting tumour-initiating cells in lung cancer**
Departement Klinische Forschung, Universität Bern, Bern
Duration: 01.10. 2013 – 30. 09. 2016

Lung cancer is the most common cause of cancer-related deaths in developed nations, having a 5-year survival rate of approximately 30 % in these countries. More than 80 % of lung tumours are non-small cell lung cancers (NSCLC). It was postulated that the propagation of tumour is mediated by so-called tumour-initiating cells. Those cells can self-renew as well as differentiate to give rise to the majority of the cells in the tumour. In NSCLC, tumour-initiating cells were identified and subsequent analysis indicated that a specific enhancement of the metabolism drives tumour-initiating cells growth and tumourigenesis. Those cells showed enhanced glycine decarboxylase activity as well as a deregulation of the DNA damage response signalling pathway, the pathway responsible to repair the DNA. This study aims at identifying key proteins of the DNA damage response pathway that are deregulated in NSCLC tumour-initiating cells. This approach might identify novel targets for pharmacological or genetic intervention to treat lung cancer.

Müller Loretta | **Carcinogenic potential of gasoline car exhaust (including nanoparticles) and their effect on natural killer cells**
Departement Klinische Forschung, Universität Bern, Bern
Duration: 01. 06. 2013 – 31. 05. 2016

The majority of cars in Switzerland are gasoline cars, but – in contrary to diesel exhaust – little is known about potential adverse health effects of gasoline exhaust emissions. In addition, new gasoline technologies and aftertreatment systems (e. g. particle filter) have recently been introduced on the market, making investigations about potential impacts of gasoline exhaust on the human health timely. Most of the emitted particles are nanoparticles, meaning particle between 1 and 100 nanometres in size, and contain various known or potential carcinogens. Since the emitted particles are extremely small, they can easily penetrate into cells.

Respiratory epithelial cells are among the first cells in the respiratory system to be exposed to inhaled air pollutants and are considered as the switchboard between the respiratory system and immune response. They are affected by exhaust emissions and interact with immune cells, such as natural killer cells. Furthermore, they are the cells that are mainly affected in the development of lung cancer. Natural killer cells are cells of the immune system important for fighting against infections. This project will investigate the carcinogenic potential of gasoline car exhaust on two different levels. First, direct effects on epithelial cells and on bacteria will be tested. Secondly, we will test whether the functionality of natural killer cell may be impaired by gasoline car exhaust which could make the development of tumours more likely

Sandzeichnung, Videostill, 2012

Peng Ren-Wang | **Functional identification and molecular targeting of human lung cancer stem cells**
Departement Klinische Forschung, Universität Bern, Bern
Duration: 01.01.2014–31.12.2014

Lung cancer is the number one cause of cancer lethality worldwide, with an overall 5-year survival rate of about 10 %. This poor prognosis is due to therapeutic resistance and tumour recurrence. Precisely how resistance and recurrence occur is unknown. Recent data indicate that tumour initiation, sustained growth and recurrence could be attributed to a subset of cancer cells: the cancer stem cells. Those cells might also be responsible for resistance to chemo- and radiotherapy, making the targeting and permanent incapacitation of cancer stem cells a promising strategy for next-generation anti-cancer therapy. The identity of human lung cancer stem cells remains controversial. In addition, whether and how lung cancer stem cells are connected with resistance to chemotherapy and whether cancer stem cells prevalence is associated with the poor prognosis of lung cancer is unclear. The goal of this project is to identify the cancer stem cells subset in non-small cell lung cancer – the most common type of lung cancer – to elucidate the molecular signature of cancer stem cells and characterize vulnerabilities of these cells for therapeutic intervention.

Schäfer Stephan | **Molecular characterization of adenosquamous carcinoma of the lung as a prime type model of tumour heterogeneity**
Institut für Pathologie, Universität Bern, Bern
Duration: 01.01.2014–31.12.2014

Adenosquamous carcinoma of the lung is a distinct subtype of non-small cell lung cancer that accounts for about 4 % of all lung cancers. It is defined by the coexistence of both adenocarcinoma and squamous cell carcinoma components. In this regard, adenosquamous carcinoma can be seen as a prime example of tumour heterogeneity. Tumour heterogeneity means that different tumour cells within one tumour show distinct morphological profiles. As the search for therapeutically relevant genetic alterations is directed by the morphological subtype, adenosquamous carcinomas of the lung and tumour heterogeneity in general pose a problem. Indeed, small biopsies are used for molecular analysis in advanced tumour stages are potentially prone to sampling errors, which might result in inadequate treatment. Understanding of tumour heterogeneity is of utmost importance and will allow a better understanding of the causes and progression of the cancer.

The aim of this study is the molecular characterization of adenosquamous carcinoma of the lung, focusing on therapeutically relevant mutations. In addition, we aim at identifying alterations that are specific for either component

and to compare our results to pure adenocarcinoma and squamous cell carcinoma of the lung. The results will enhance the understanding of the molecular basis of morphological differentiation and resistance emergence in the context of targeted therapy.

Schlapbach Christoph | **Characterizing human interleukin 9-producing T-helper memory cells and their role in anti-tumour immune response in malignant melanoma**
Universitätsklinik für Dermatologie, Inselspital, Universitätsspital Bern, Bern
Duration: 01.10.2013 – 30.09.2014

Human T-helper (TH) cells are crucial mediators of the immune system. They help the activity of other immune cells by releasing T-cell cytokines, which are small proteins important for signalling. To respond to the myriad of infectious and non-infectious challenges, they have evolved into functionally distinct subsets such as TH1, TH2, etc. TH9 cells produce a specific cytokine called IL-9. Those cells have recently been proposed as a novel subset of T-helper cells and studies in animal models suggest that they play a protective role in tumour immunity. However, studies of human TH9 cells are lacking.

Recent studies in mice have shown that IL-9 promotes robust anti-tumour immune responses against melanoma and other cancers. These promising results put TH9 cells in the limelight for novel approaches in cancer. However, the role of TH9 cells in human melanoma remains to be investigated. Our preliminary data indicate for the first time the existence of human TH9 cells, thus raising the possibility to address important questions regarding their identity and functional properties. In addition, we found large numbers of IL-9 expressing cells in the immune infiltrate of human melanoma, thus warranting further investigation of the role of TH9 cells in the human anti-melanoma immune response. The overarching aim of this project is to investigate the identity and properties of human TH9 cells and their role in the anti-melanoma immune response.

Schucht Philippe | **Extent of resection thresholds as predictor of survival in patients with glioblastoma**
Universitätsklinik für Neurochirurgie, Inselspital, Universitätsspital Bern, Bern
Duration: 01.07.2013 – 30.06.2017

Glioblastoma is a malignant, locally invasive brain tumour whose prognosis remains grim despite various improvements in treatment. In the past, radical surgery was met with scepticism due to the aggressive infiltrative character of the tumour. However, an increasing number of retrospective studies over the last decade reported a prolonged overall survival after more extensive resection. Thus, the removal of majority of the tumour – the contrast enhancing part of it – has become a major aim of surgical treatment. Extending surgery from mere biopsies towards radical resections of contrast enhancing tumour requires costly technical assistance and carries risks of neurological deficits if the tumour has infiltrated functionally intact brain areas.

In recent years we have developed in Bern refined methods to increase the safety of radical surgery. The crucial question is, however, whether and to what extent radical resection prolongs survival. This study will investigate this question. After a homogenous group of patients is generated, the surgeon will perform surgery. In some case radical resection will be achieved in others it will not. It must be stressed that in contemporary neurosurgery small remnants after resection are still considered as a good result as long as more than 90 to 95 % of the tumour bulk is resected. We will analyse whether there is a difference in survival in the two groups where surgery was performed, meaning whether there is a correlation between radical surgery and better outcome.

Central Switzerland Cancer League

Diebold Joachim | **Do the new possibilities for targeted therapy lead to an improvement in survival rates of advanced lung cancer patients in Central Switzerland?**
Zentralschweizer Krebsregister, Luzerner Kantonsspital, Luzern
Duration: 01.01.2011 – 31.12.2013

Based on the numbers from the Cancer Registry of Central Switzerland, we will examine the following questions: in how many patients are the new targeted therapies an option at all? How many patients are effectively treated with the new treatment in question? And will this new therapy lead to an improved survival? The correlation of the cancer registry data with the histopathological findings and the genetic analysis will lead to an information gain that will contribute to the correct application of the new targeted therapies and to an improved patients' prognosis.

Eastern Switzerland Cancer League

Ludewig Burkhard | **Systems biology approach to molecularly characterize the lung cancer microenvironment**
Institut für Immunbiologie, Kantonsspital St. Gallen, St. Gallen
Duration: 01.01.2012 – 31.12.2015

Tumour cells display distinct genetic alterations that permit their unrestricted growth. In contrast, stromal cells that provide the growth scaffold and nutrients for the tumour most likely exhibit universal signatures that determine their function. The aim of this project is to gain novel knowledge on stromal cells that determine the growth-supporting micro-environment of lung cancer. Researchers at the Cantonal Hospital St. Gallen have developed unique tools and methods to label, characterize and molecularly ablate lung cancer stromal cells. We expect that our research will identify critical target structures on lung cancer stromal cells and that this knowledge will foster the development of novel diagnostic and therapeutic avenues.

Ansari Marc | **Association of a CTH gene variant with veno-occlusive disease in children receiving busulfan before haematopoietic stem cell transplantation**
Département de pédiatrie, Hôpitaux universitaires de Genève (HUG), Genève
Duration: 01.01.2013 – 31.12.2014

Haematopoietic stem cells (HSC) reside in the bone marrow and have the unique ability to give rise to all of the different mature blood cell types. HSC transplant are now being used for the treatment of malignant diseases, such as leukaemia as well as non-malignant diseases. Most patients respond well to the transplant; unfortunately not all. It is impossible to predict which patients are going to develop complications or relapse after an HSC transplant. However, it has been observed that clinical outcome is related to the conditioning treatment given to patients prior to the transplant. Conditioning treatments are important because they eliminate the existing cancerous cells and reduce the immune response, allowing for better engraftment of the donor stem cells.

Busulfan is one of the main drugs used in this conditioning regiment and it has been observed that patients exposed to high busulfan levels are more at risk of a worse clinical outcome, while low drug levels correlate with relapse of the disease. Varying exposure of busulfan is currently being controlled by adjusting for age and weight, but there are still 20 % of patients who suffer life-threatening adverse effects or relapse. We believe that genes, which make proteins involved in busulfan's elimination from the body, may influence this variability as busulfan might be eliminated faster or slower, allowing to more or less effect of the drug, depending which genes are expressed.

Thus our hypothesis is that genes involved in busulfan's elimination and function will aid in predicting who is going to need higher or lower doses and provide a better clinical outcome from the transplant. Our objective is to identify which genes will be the most useful at predicting a better outcome after a transplant where the patient has had a busulfan conditioning regimen.

Cohen Marie | **Novel therapeutic approaches against ovarian cancer recurrence**
Département de gynécologie et d'obstétrique, Hôpitaux universitaires de Genève (HUG), Genève
Duration: 01.01.2012 – 31.12.2014

Ovarian cancer affects 600 to 700 women each year in Switzerland. It is the leading cause of death among gynaecological cancers. Most ovarian cancers are diagnosed at an advanced stage of the disease, when the survival rate is very low. At an advanced stage, standard treatment is cytoreductive surgery followed by chemotherapy. Following this, most patients enter remission, but unfortunately most of them relapse. One strategy to reduce mortality from ovarian cancer would be to minimize relapse using targeted therapy after standard treatment.

The glucose-related protein 78 (GRP78) is a chaperone protein involved in the folding of proteins required for the survival of stressed cells such as cancer cells. GRP78 is suspected to induce tumour cell invasion and appears to play a critical role in certain cancer cells' resistance to chemotherapy. This protein is localized in the endoplasmic reticulum, but it is also observed on the surface of cancer cells and thus could be a "tumour-associated antigen". We have recently shown the presence of anti-GRP78 auto-antibodies in the serum of ovarian cancer patients. These antibodies promote apoptosis and decrease the invasiveness of cancer cells. Membrane localization of GRP78 specifically in cancer cells suggests that it may be a therapeutic target. That is why we propose to develop a targeted treatment combining photodynamic therapy, chemotherapy and immunotherapy to fight the recurrence of ovarian cancer. For this purpose, we will use vectors that are loaded with anti-cancer and/or photosensitizer agents and are covered with antibodies recognizing the same epitopes as the antibodies purified from serum of ovarian cancer patients. The drugs and/or photosensitizers will be encapsulated into the vectors.

Curran Joseph | **The 5'UTR fingerprint: a new diagnostic marker for breast cancer**
Département de microbiologie et médecine moléculaire, Université de Genève, Genève
Duration: 01.01.2013 – 31.12.2015

Breast cancer is the second most commonly diagnosed cancer in the world. It is aetiologically and genetically heterogeneous. As a consequence there is a continual need to establish new genetic markers that will aid in tumour typing, assist in evaluating the risk of recurrence and provide signatures that can guide therapies. In a pilot study in which we compared the transcriptome from a breast tumour cell line and a non-tumoural control, we observe cell type specific heterogeneity in the 5' untranslated region of nearly 100 genes. Many of these are known to play central roles in cell growth control and a number have already been associated with breast cancer. These changes alter the protein readout and may serve as a molecular fingerprint of the tumoural phenotype. The proposal aims at establishing if this fingerprint has potential as a diagnostic marker for breast cancer.

Dietrich Pierre-Yves | **Identification and validation of glioma antigen: towards immunotherapies for brain tumours**
Service d'oncologie, Département de médecine interne, Hôpitaux universitaires de Genève (HUG), Genève
Duration: 01.01.2011 – 31.12.2013

For more than 10 years, the goal of our research is to better understand how our immune system can defend us against the development of tumours in the brain and, on this basis, to develop new therapeutic strategies such as immunotherapies. Triggering an effective immune response and using lymphocytes as "killer cells" targeting tumour cells seems realistic, but it is essential that this response is selective, meaning that the lymphocytes kill specifically tumour cells, while leaving the normal cells of

the brain untouched. Up to now, this selectivity seemed impossible in the absence of structures (called antigens) selectively expressed by tumour cells (and not expressed on normal cells).

This is no longer the case. Indeed, thanks to collaboration with a spin-off of the University of Tübingen (Immatics), we have identified 10 interesting glioma antigens. The goal of this project is to characterize these antigens to ensure that they are (1) overexpressed by tumour cells (almost no expression on normal cells should greatly reduce the risk of autoimmunity and toxicity); (2) immunogenic, meaning capable of eliciting an immune response, not only in healthy individuals but also in glioma patients; and (3) expressed in glioma stem cells, which play an essential role in the resistance of cancers to standard therapies (radiotherapy, chemotherapy). We hope to confirm that these glioma antigens are ideal targets for future immunotherapies in both vaccine and cellular therapy strategies.

Irminger Irmgard | **Regulation of the oncogenic isoforms of the tumour suppressor BARD1 in cancer by microRNAs and non-coding RNAs**
Département de gynécologie et d'obstétrique, Hôpitaux universitaires de Genève (HUG), Genève
Duration: 01.01.2012 – 31.12.2013

BARD1 is the constitutive partner of BRCA1, some mutations of which predispose to breast cancer. The ubiquitin ligase activity of BARD1-BRCA1 has a role in numerous onco-suppressor functions, especially within the cell cycle, in regulating the transcription and distribution of damaged DNA. The expression of different isoforms of BARD1, the outcome of alternative splicing, is incriminated in breast, colon, and lung cancers. Studying the mechanisms regulating BARD1 expression is therefore of key importance.

Our preliminary findings showed that the microRNA miR-203 regulates the expression of BARD1 in cancer cells. MicroRNAs are thought to be important regulators of carcinogenesis and may be used clinically as biomarkers and agents or as therapeutic targets. We have discovered a new non-coding isoform of BARD1 (9'L) expressed in cancer cells. Its expression is correlated to the expression of other BARD1 isoforms; it is significantly overexpressed in cancer tissues. We therefore hypothesize that RNA 9'L inhibits tumour-suppressor microRNAs and induces the expression of oncogenic isoforms of BARD1. This microRNA regulatory mechanism by "decoy" RNAs had been described only recently and appears to play a significant role in carcinogenesis.

In this project, we aim at evaluating in greater depth the role of miR-203 and other microRNAs in the regulation of BARD1. We will confirm the decoy RNA properties of 9'L and evaluate its functions in the regulation of BARD1 and microRNAs. We will also evaluate the diagnostic utility of 9'L and miR-203 for the clinical care of patients in a large cohort. Finally, we will extrapolate our research findings into a trial for clinical application. The research project described here is therefore not only of fundamental scientific value for future cancer biology but will also enable the uptake of its results for the promotion of innovative clinical methods.

Le Gal Frédérique | **Skin cancer screening using high-sensitivity infrared imaging**
Département des spécialités de médecine, Service de dermatologie et vénérologie, Hôpitaux universitaires de Genève (HUG), Genève
Duration: 01.01.2013 – 31.12.2014

Incidence of skin cancers is very high in Switzerland and rising worldwide. Their prognosis depends on the precocity of diagnosis. Detection of skin cancer is essentially clinical and greatly depends on the clinician's expertise. Though, as early tumours often lack specific signs, many benign lesions are excised to be on the safe side. Moreover some skin cancers do not have visible limits, which can induce complex or multistep surgery. Therefore, detection and treatment of these tumours generate big health costs. Compared to benign lesions, malignant tissue has specific thermal properties that can be exploited to diagnose skin cancer. In collaboration with the Zurich University of Applied Sciences (Zürcher Hochschule für Angewandte Wissenschaften, ZHAW), we plan to optimize and test a new highly sensitive infrared imaging device to detect skin cancers and define their actual limits. Lock-in thermography is an objective non-invasive method that can optimize the management of skin cancers and reduce its costs.

Le Gal Frédérique | **Beta-blockers in the adjuvant treatment of melanoma, an interventional clinical study**
Département des spécialités de médecine, Service de dermatologie et vénérologie, Hôpitaux universitaires de Genève (HUG), Genève
Duration: 01.01.2013 – 31.12.2014

Malignant metastatic melanoma is the leading cause of death among skin cancer patients and its incidence is increasing worldwide. Despite recent advances in the identification of recurrent mutations linked to melanoma and the development of new drugs targeting these mutations, no long-term treatment is currently available to efficiently improve the dramatic outcome of this disease. Our project is based on recent retrospective studies on human melanoma patients and experiments we conducted in animals xenografted with human melanoma cells which suggest that beta-adrenergic antagonist's treatment effectively improve the survival of patients with malignant melanoma. Our study attempts to understand the mechanisms governing beta blockers action on melanoma by identifying the targets of these molecules, the signalling pathways involved, and the regulation of tumour development. We will now investigate the benefit of an adjuvant treatment with propanolol on melanoma progression in a clinical trial.

Mandriota Stefano | **The ATM/p53 signalling pathway in the regulation of cellular senescence**
Département de pédiatrie, Division d'onco-hématologie, Hôpitaux universitaires de Genève (HUG), Genève
Duration: 01.01.2012 – 31.12.2014

The p53 tumour suppressor protein plays a key role in the induction of cellular senescence, which is an important barrier to cancer development. However, very little is known about the physiological mediators of cellular senescence induced by p53. CEACAM1 is an immunoglobulin superfamily member whose expression is frequently lost in human tumours and exhibits tumour suppressor features in several experimental systems including CEACAM1 knockout mice.

There is currently little understanding of the pathways and mechanisms by which CEACAM1 exerts its tumour suppressor function. We recently found that CEACAM1 is strongly upregulated during the cellular response to DNA double strand breaks (DSBs) and that upregulation is mediated by the ataxia telangiectasia mutated (ATM)/p53 pathway. Stable silencing of CEACAM1 showed that CEACAM1 is required for the induction of p53-mediated cellular senescence in response do DNA damage. These findings identify CEACAM1 as a key component of the ATM/p53- mediated cellular response to DNA damage and as the first established tumour suppressor gene mediating cellular senescence downstream of p53.

In this project, we propose to further elucidate the role of CEACAM1 in the induction of cellular senescence. In view of the novelty of the identification of CEACAM1 as a component of the ATM/p53 regulated DNA damage response and the well-defined features of CEACAM1 as a tumour suppressor, we strongly feel that the proposed project will provide important and fertile new insights into p53 and CEACAM1 tumour suppressor function and into the regulation of cellular senescence.

Martinou Jean-Claude | **Role of the mitochondrial pyruvate carrier in the proliferation and metastasis of breast cancer cells**
Département de biologie cellulaire, Faculté des sciences, Université de Genève, Genève
Duration: 01.01.2013 – 31.12.2014

Many cancer cells are known to consume high amounts of glucose, which they transform into pyruvate, then into lactate, thereby producing energy without involving the mitochondria. This process is classically called the "Warburg effect". Although frequent, this process does not apply to all tumours. This is the case for a number of breast cancers, in which pyruvate, the end-product of glycolysis, is not transformed into lactate but rather transported into mitochondria. There, pyruvate is further oxidized allowing production of energy through oxidative phosphorylation. Until recently the molecular identity of the mitochondrial pyruvate carrier was unknown. We have recently identified this carrier, which plays a key role in cell metabolism. Importantly, this carrier has been found to be highly expressed in some breast cancers. In this research proposal, we propose to investigate the role of the mitochondrial pyruvate carrier in tumour cell proliferation and metastasis.

Preynat-Seauve Olivier | **Identification of miRNA targets for glioblastoma using a novel *in vitro* model**
Laboratoire d'immuno-hématologie transfusionnelle, Hôpitaux universitaires de Genève (HUG), Genève
Duration: 01.01.2013 – 31.12.2015

Glioblastoma multiforme (GBM) is the most common primary brain tumour in adults and represents one of the most aggressive human cancers. MicroRNAs (miRNAs) open an exciting and promising area for the development of new therapeutic targets. They regulate a high number of mRNA transcripts and, consequently, represent a key molecular checkpoint in the control of biological processes. Based on the use of stem cells, our team has recently developed an *in vitro* model of human GBM development within a human brain-like tissue with a high degree of similarity to the *in vivo* cancer development in patients. We then took advantage of this system to analyse the entire microRNome through an ultra-deep sequencing. The main objectives were to identify: (1) miRNAs induced or upregulated when the tumour interacts with brain-like tissue and (2) miRNAs specifically expressed in GBM patients. Using this approach, we identified new miRNAs not previously described in GBM. We propose to study the impact of the modulation of these novel miRNAs on GBM aggressiveness and resistance to drugs and radiation with the goal of proposing new therapeutic targets.

Reith Walter | **Identifying the cellular functions and regulatory networks that underlie the link between microRNA-155 and cancer**
Département de pathologie et d'immunologie, Faculté de médecine, Université de Genève, Genève
Duration: 01.01.2012 – 31.12.2014

MicroRNAs constitute a class of small, single-stranded, non-coding and well-preserved RNAs. By binding to target messenger RNAs, they cause them to be broken down or silence their ability to translate proteins. Post-transcriptional regulation by these microRNAs is involved in a great variety of essential physiological functions as well as in several diseases, in particular in the onset and development of cancer. MicroRNA-155 (miR-155) has been implicated in the development of cancer, but the target genes of this microRNA have yet to be identified.

The objective of this study is to attain a better understanding of the link between miR-155 and cancer by shedding light on its biological functions and its target genes in dendritic cells (DCs). Recently we studied the role of microRNAs in the differentiation, maturation and function of DCs. We showed that activation of miR-155 is a general and preserved characteristic in the maturation of DCs. Moreover, analysis of DCs in knockout mice for miR-155 revealed that induction of miR-155 is necessary for the maturation of DCs. Using functional approaches and genomic analyses, we demonstrated that the c-Fos transcription factor is a direct target of miR-155 and that its expression needs to be suppressed in order for DCs to mature.

In future experiments, we suggest studying in detail the expression, enzyme activity and regulation of a new potential target of miR-155: arginase 2. In view of the known role of arginase in tumour progression and development, we will investigate the consequences of deregulating its expression, in particular on T-cell activation and proliferation. These studies should enable us to gain a better understanding of the mechanisms controlled by miR-155 in tumour development.

Thore Stéphane | **Steroid receptor RNA activator: a new target for modulating the hormonal response in cancer cells**
Département de biologie moléculaire, Faculté des sciences, Université de Genève, Genève
Duration: 01.01.2011–31.12.2013

Specific cancers of some organs, such as those affecting the breast, pancreas or colon, share a common feature: their growth and dangerousness are closely dependent on the presence of a number of hormones. Studying the impact of these hormones on the physiology of the cell, whether healthy or cancerous, is therefore of prime importance. These studies will enable us to develop treatments that target biological mechanisms identified as being hormone-dependent and thus to be more effective at eliminating cancer cells. In the past decade, it has been shown that the regulation of transcription by hormone receptors is one of the fundamental hormone-linked mechanisms. In studies on the regulation of transcription by hormones, an RNA known as steroid receptor RNA activator (SRA RNA) was shown to have a modulator role, being able to amplify or inhibit the action of hormones on transcription. This RNA is the first of its kind to display an action of this type, which alone represents a new level for the hormone-based regulation of activation pathways.

Obtaining molecular models that describe the specific association of SRA RNA with various nuclear hormone receptors or partners involved in the cell response to hormones is essential for our understanding of its action. Moreover, these atomic models may be used to identify and/or develop molecules able to modify its action. Thanks to these research programmes, we will have greater means at our disposal for combating hormone-positive cancers. Newly identified molecules of this kind could be used alone or in combination, thereby limiting the possibilities that the cancer cells might develop resistance capabilities, a recurrent problem in cancer treatment.

Tille Jean-Christophe | **Role of heparan sulfate in endometrioid carcinoma: tissue remodelling, angiogenesis and lymphangiogenesis**
Département de pathologie clinique, Faculté de médecine, Université de Genève, Genève
Role of heparan sulfate in endometrioid carcinoma: tissue remodelling, angiogenesis and lymphangiogenesis
Duration: 01.01.2011–31.12.2013

Angiogenesis and lymphangiogenesis enable the formation of new blood and lymph vessels in the endometrium in a process that occurs physiologically during the ovarian cycle and pathologically in tumour growth. Heparan sulphate anti-coagulants bind and activate anti-thrombin such as heparin. They are present in the endothelial basement membrane and endow healthy endothelium with anti-thrombotic properties. The distribution and modulation of heparan sulphate anti-coagulants during tissue plasticity are not known. They appear to be reduced under the pathophysiological conditions that permit cellular invasion of the tissues. We are investigating the function of heparan sulphate anti-coagulants in vascular and tissue plasticity during tumour invasion of the endometrium *in vivo* and *in vitro*. The data obtained in this study will enable evaluation of the therapeutic potential of heparan sulphate anti-coagulants as modulators of tissue invasion in endometrial cancer.

Wehrle-Haller Bernard | **Kinase-independent functions of the receptor tyrosine kinase c-kit in the persistence and adhesion of cancer stem cells to their environmental niche**
Département de physiologie cellulaire et métabolisme, Centre médical universitaire (CMU), Genève
Duration: 01.01.2012–31.12.2015

Leukaemia are cancers of the blood that often develop resistance against drugs that block the enzymatic activity required for cell proliferation and cancer growth. One hypothesis for the observed resistance against these treatments is the capacity of tumour cells to switch back into a dormant state, by crawling into environmental niches in which they can survive without being stimulated to divide. This crawling process is also responsible for the formation of tumour metastasis. The process of crawling, or niche-adhesion is regulated by two types of adhesion systems that synergize in such a way that they function even in the absence of the critical enzymatic activity required for tumour cell proliferation. Here in this grant, we propose to explore the mechanisms of this crawling and adhesion mechanism and would like to develop an experimental system to test whether the forced exit of tumour cells from their niches can restore there sensibility to therapy.

Thurgau Cancer League

Fleischmann Achim | **Promotion of cancer research, focused on the area of gynaecological and urological tumours**
Pathologie, Kantonsspital Münsterlingen, Münsterlingen
Duration: 01.01.2014 – 31.12.2015

This project focuses on prognostic and predictive biomarkers in urological tumours, especially in metastatic bladder and prostate cancers. These tumours are relatively frequent and make it possible to more accurately characterize the lethal tumour components, namely the metastases. Initially the prognostic significance of histopathological tumour characteristics and key figures of the surgical procedure will be investigated. The group of uropathology will evaluate subsequent tumour markers at the cellular, protein, DNA and microRNA level in relation to tumour heterogeneity, prognostic relevance and predictive potential as well as tumour regression by bladder cancer after chemotherapy. These studies will allow to assess the prognosis of the disease, to plan individual adjuvant therapies and to better understand processes in metastasis. The project consists of a collaboration with various national and international research groups.

Legler Daniel | **Breast cancer project**
Biotechnologie Institut Thurgau, Universität Konstanz, Kreuzlingen
Duration: 01.01.2013 – 31.12.2016

The latest findings from the current research at the Biotechnology Institute Thurgau suggest that a new signalling pathway was discovered, which seems to be responsible for the efficient migration of breast cancer cells in the lymph nodes and thus for metastasis. This project aims at investigating whether a naturally occurring mutation may serve as a diagnostic marker for breast cancer and on the other hand to explore the role of the newly discovered signalling pathway on cell migration and metastasis of breast cancer cells.

Reuter Christiane | **Study of intraoperative radiotherapy of the breast**
Radioonkologie, Kantonsspital Münsterlingen, Münsterlingen
Duration: 01.01.2013 – 31.12.2014

After breast-conserving surgery, the remaining breast tissue should be irradiated to reduce the risk of intramammary recurrence by a factor of 3 to 4. The irradiation of the operated breast must be in frequent small doses to cause as few side effects as possible. Therefore, a postoperative irradiation of the breast lasts five to six weeks with daily irradiation sessions, where on one side the whole breast tissue is irradiated and on the other hand, the tumour is specifically irradiated (boost). In order to shorten the exposure time and to irradiate the targeted tumour specifically, an intraoperative irradiation was developed. Surgeons place a spherical radiation source intraoperatively in the excision and the irradiation is performed under control of the radio-oncologist during the operation, resulting in an anaesthesia time that is extended by about 40 minutes. These intraoperative irradiations eliminate the need for boost irradiation, decreasing the postoperative radiotherapy by at least one week. In a strictly defined patient group with low risk the intraoperative radiotherapy will replace the postoperative radiotherapy altogether.

The radiation oncology division of the Hospital Thurgau AG began an observational study that will track accurately whether with intraoperative irradiation relapse rates, cure rates, side effects, quality of life, and cosmetic is better than with standard radiotherapy alone. To this end, photos of patients will be evaluated by a computer programme and the quality of life will be determined using questionnaires. In order to do this project, it is necessary to operate a database and to appoint a study coordinator. The Thurgau Cancer League supports scientific work aiming at the monitoring and the evaluation of the study. The patients of the canton Thurgau will be monitored very closely in the application of this new radiotherapy method allowing for the evaluation of this method.

Ticino Cancer League
(Fondazione ticinese per la ricerca sul cancro)

Catapano Carlo | **Non-coding RNAs and epigenetic networks in prostate cancer pathogenesis and novel therapeutic strategies**
Istituto oncologico della Svizzera italiana (IOSI), Bellinzona
Duration: 01.01.2013 – 31.12.2013

Prostate cancer is the most common cancer in the male population in Western countries. Obviously, there is a need to find novel diagnostic and prognostic biomarkers and more effective treatment strategies. Several genetic factors are known to contribute to the development of prostate cancer, but we know that there are also external (so called epigenetic) factors, which might modulate the expression of the genetic defects. Those epigenetic processes are known to have an impact on tumours' initiation and progression. In this study we intend to identify novel so-called noncoding RNAs (small structures of ribonucleic acid), which might play an important role in the development of prostate tumours. We will do that in prostate tumour cell lines, but also in tumour biopsies. We hope that this study will help developing some new therapeutic approaches to this cancer, mainly in cases resistant to endocrine treatment.

Ceppi Francesco | **Post-graduate training in paediatric oncology**
Hôpital Notre-Dame, Montréal, Canada
Duration: 01.01.2013 – 31.12.2013

Francesco Ceppi finished his training as paediatric oncologist in Lausanne and is now specializing in some aspects of the treatment of childhood cancer in Canada.

Civenni Gianluca | **Isolation of stem cells from human prostate biopsy to study tumour initiation**
Istituto oncologico della Svizzera italiana (IOSI), Bellinzona
Duration: 01.01.2013 – 31.12.2013

Prostate cancer is the most common cancer in men in Western countries. However, its origin remains not well understood. The clinical evaluation of prostate cancer is very heterogeneous: in some cases it is very favourable, while other patients will die rather rapidly due to metastasis generated by the prostate cancer. It has been postulated, that this very different behaviour might be related to different characteristics of the stem cells in different cases of prostate cancer. In our study we will try to isolate stem cells both from normal prostatic tissues as well as from biopsies obtained in patients suffering from prostate cancer. By comparing the biological characteristics of these stem cells, we hope to be able to gain new insights into the biology of prostate cancer, which might in turn generate new therapeutic approaches.

Frattini Milo | **Investigation of the role of NEU3 in colorectal carcinogenesis**
Istituto cantonale di patologia, Locarno
Duration: 01.01.2013 – 31.12.2013

In recent years we made progress in the treatment of colorectal cancer. We know that response to different treatments varies depending on the expression of EGFR (epithelial growth factor receptor), but we do not know which factors can modulate the expression of EGFR. In this study, we will evaluate the potential role NEU3 (an enzyme) in modulating the expression of EGFR in cell lines. In addition, we will try to understand the conditions under which new targeted therapies may be more active depending on the expression of EGFR and NEU3.

Molinari Francesca | **Identification of new alterations in the small intestine adenocarcinoma through new sequencing methodology**
Istituto cantonale di patologia, Locarno
Duration: 01.01.2013 – 31.12.2013

Adenocarcinomas of the small intestine represent a rare tumour with an aggressive clinical behaviour. Surgical intervention is the main treatment, but unfortunately no effective standard chemotherapy has been established that would prolong survival of patients. So far, the molecular alterations involved in the development of this tumour have been only marginally investigated, limiting the possibility to discover genetic lesions, which might become the target for new treatments. In this study, alterations occurring in a cohort of patients affected by this tumour will be investigated with a new methodology for genetic profiling, which is able to analyse simultaneously hundreds of mutations occurring in cancer-associated genes. Importantly, this can be done also on fixed material, which is already present at our institute. The definition of this, so far, unknown genetic lesions could prompt the development of more targeted treatment for this rare form of tumour.

Zurich Cancer League

Bernasconi Michele | **Role of proprotein convertases in paediatric sarcomas: useful theragnostic targets?**
Experimentelle Infektiologie und Krebsforschung, Kinderspital Zürich, Universitäts-Kinderkliniken, Zürich
Duration: 01.01.2011 – 31.12.2013

The treatment of childhood cancer has specific requirements, because excessive use of chemotherapy and especially radiotherapy can lead to significant long-term sequelae. Next to the development of entirely new therapeutic options, one of our objectives is to identify new therapeutic targets. We have identified a family of proteases (proteolytic enzymes) that play an important role in the growth of paediatric sarcomas. We will investigate the role of these proteases in paediatric sarcomas in order to use them as targets for new therapies. In this project, we hope to be able to develop new protocols for the treatment of paediatric sarcomas with fewer side effects.

Bornhauser Beat | **Large scale drug response profiling to identify new targets in refractory leukaemia**
Forschungsgruppe Leukämie/Onkologie, Kinderspital Zürich, Universitäts-Kinderkliniken, Zürich
Duration: 01.01.2011 – 31.12.2013

Treatment of relapsed childhood leukaemia is a major challenge. Using a microscope-based analysis platform, we record systematically the response of leukaemia samples to a variety of new therapeutic substances and compare these profiles with genetic information in order to identify specific patterns. We hope to develop new therapies for the treatment of relapsed patients.

Graf Rolf | **Inflammation contributes to the regression of acinar-to-ductal metaplasia in the injured pancreas**
Klinik für Viszeral- und Transplantationschirurgie, Universitätsspital Zürich, Zürich
Duration: 01.01.2013 – 31.12.2013

Tissue damage occurs during a pancreatitis, which is amplified by inflammation. Nevertheless, the pancreas heals by regenerative processes, during which the cells change dramatically and form cancer-like structures. Preliminary results show that inflammatory factors have a positive effect on the changed pancreatic cells.

Hottiger Michael | **Assessment of ADP-ribosylomes to identify specifically ADP ribosylated proteins that regulate PARP inhibitor sensitivity of cancer cells**
Institut für Veterinärbiochemie und Molekularbiologie, Universität Zürich, Zürich
Duration: 01.01.2013 – 31.12.2015

The goal of this project is to determine all of the ADP-ribosylated proteins in PARP inhibitor-sensitive and non-sensitive cell lines with newly developed methods and thereby to identify proteins, which should improve the individualized use of PARP inhibitors in future cancer therapies.

Sandzeichnung, Videostill, 2012

Müller Anne | **Epigenetic silencing of tumour suppressor genes in the pathogenesis of diffuse large B-cell lymphoma**
Institut für Molekulare Krebsforschung, Universität Zürich, Zürich
Duration: 01.01.2013 – 31.12.2015

The goal of the project is to investigate the functional impact of newly identified epigenetically silenced putative tumour suppressor genes in diffuse B-cell lymphoma *in vitro* and *in vivo*.

Münz Christian | **Boosting of NY-ESO-1-specific re-directed T-cells**
Institut für Experimentelle Immunologie, Universität Zürich, Zürich
Duration: 01.01.2013 – 31.12.2014

With the infiltration of monoclonal antibodies in T-cells, the cells can be reprogrammed and therefore specifically directed against tumour cells. The efficiency of this new immunotherapeutic approach will be testes in so-called humanized mice, i. e. mice with a human immune system.

Nadal David | **Natural killer cell control of Epstein-Barr virus-induced cancerous B-cell transformation**
Abteilung Infektiologie und Spitalhygiene, Kinderspital Zürich, Universitäts-Kinderkliniken, Zürich
Duration: 01.01.2013 – 31.12.2013

We are investigating how the body's own natural killer cells prevent the formation of Epstein-Barr virus-related cancers, in order to create potent therapies against this common and often deadly form of childhood cancer.

Rohrer Bley Carla | ***In vivo* profiling of DNA damage and repair kinetics after anti-neoplastic treatment: use of a minimally invasive approach**
Abteilung für Radio-Onkologie, Universität Zürich, Zürich
Duration: 01.01.2013 – 31.12.2013

This project will study the speed and amount of DNA damage formation of tumour cells after radiotherapy as well as the repair of the damage by the cell's own repair mechanism in various tumours. The goal of this profiling of DNA damage formation and repair is to provide individual prognostic information and to improve the therapy by additional measures.

Tabatabai Ghazaleh | **Thymosin beta-4 in malignant gliomas: a novel regulator of angiogenesis?**
Klinik für Neurologie, Universitätsspital Zürich, Zürich
Duration: 01. 01. 2013 – 31. 12. 2014

Glioblastoma are malignant highly-vascularized primary brain tumours. In the projects, we investigate the contribution of the thymosin beta-4 signalling pathway to vessel formation in glioblastoma.

Weber Achim | **Role of innate lymphoid cells (ILC) in intestinal inflammation and carcinogenesis**
Institut für Klinische Pathologie, Universitätsspital Zürich, Zürich
Duration: 01. 01. 2013 – 31. 12. 2014

The formation and growth of cancer cells are significantly influenced by the environment of the tumour cells. The role of a particular type of inflammatory cells, the so-called innate lymphoid cells, will be examined in a mouse model for inflammatory bowel disease (IBD) and spontaneous cancer development. Form the results we expect a better understanding of the role of these immune cells in cancer development in the context of IBD and the identification of new therapeutic approaches in IBD and colon cancer.

Genome stability, DNA repair and cancer

Cancer usually develops on a time scale of years or decades. It is a complicated and long process of normal body cells transforming into abnormal cells with several unfavourable characteristics. The transformations are genetic in nature. They are passed on from the mother cell to the daughter cell during cell division and thus spread in cell clones. Thorough exploration and investigation of the aetiology and mechanisms of these genetic processes is essential for our understanding of the nature of cancer, its development, its ability to adapt again and again to even the most adverse conditions, and also its weak spots, which can be exploited therapeutically.

Identity and alteration of cells

To understand these transformations and alterations of cells, we must recall how the normal identity of a body cell is determined. Although a great variety of types of cells having very specialized functions exist in the human body, each and every one of them carries an identical copy of the person's entire genetic blueprint in its cell nucleus. This genetic information lies in the DNA in a coded form as a specific sequence of its four chemical building blocks. Together, the more than three billion building blocks of the human genome (the complete set of genetic information coded in the DNA) contain thousands of genes that are responsible for specific biological functions.

The differentiation into different body cells occurs because for each type of cell only one certain selection of these genes is transcribed, and those are the genes that make the cell functions that are specifically needed for the organ or tissue. This cell type-specific expression of the genome is controlled by epigenetic mechanisms. Through the chemical modification of the DNA and/or its protein structure a kind of higher-level genetic code is generated that finally determines what genes can be transcribed and what genes cannot be transcribed. This epigenetic code is set based on signals from the environment during the differentiation of a cell type and is subsequently fur-

Prof. Primo Schär, PhD
Professor of molecular genetics and research group leader at the Department of Biomedicine, University of Basel

Fotogramm / Linde, 2013

ther inherited within a cell line with each cell division. Identity and function of a tissue cell are thus determined by the combined workings of two levels of genetic information: the genetic code stored in the DNA sequence and the higher-level epigenetic programming of the activity of this code.

As long as both the genetic information and also its epigenetic programming remain stable and are passed on unaltered at cell division, the normal, intended function of a cell line is preserved. But if there are alterations in the DNA sequence of a certain cell, so that gene functions are impaired or even destroyed (genetic mutations), or if there are alterations in the epigenetic programming pattern, so that genes that are supposed to be active in a cell type suddenly become inactivated or vice versa, a cell can begin to change its characteristics and can finally degenerate.

A look at the genome of cancer cells reveals that there are a number of these genetic and epigenetic alterations. These modifications typically affect cell functions that deregulate cell division and cell death in such a way that cells can grow uncontrollably. Depending on the stage of a tumour, there are further alterations, such as changes that allow the cells to circumvent the immune defence, to optimize metabolism, and to detach from the tissue of their origin and establish colonies in other parts of the body. Cancer is thus the result of progressive genetic and epigenetic instability that ultimately leads to the loss of cell identity and gives the altered cells a high level of adaptability (plasticity) and thus a selective advantage over normal body cells. For this reason, one of the central questions in cancer research is why such changes occur and whether we can stop them.

The (in)stability of the (epi)genome

Genetic mutations arise mainly as a result of DNA damage and/or replication errors in the process of producing two replicas of the DNA before cell division. Chemically, DNA is a very large, relative reactive molecule that in the surrounding of the cell nucleus is exposed to effects of many chemical reactions (such as oxidation, hydrolysis, or modification through by-products of cell metabolism). In addition to this endogenous type of DNA damage, there is also DNA damage caused by environmental factors: Well-known examples include ultraviolet components of sunlight, ionizing radiation, tobacco smoke, and a number of chemical substances, including some prominent chemotherapy drugs like the various derivatives of cisplatin. Measurements show that the DNA damages occur in our cells more than 50,000 times per day per cell. The majority of these are caused by cell-internal processes; the frequency and severity of environmentally caused damages vary greatly depending on the amount of exposure. All of these sources can have a mutagenic effect and/or alter epigenetic modification patterns.

DNA damages impair in different ways the structure and function of DNA as a genetic master copy. Without the cellular control and repair systems, these damages would in most cases lead to errors in the transcription of DNA during DNA replication and, through this, result in genetic mutations. However, cells put a lot of work into protecting their genome. They have a complex network of specialized functions and mechanisms to detect and eliminate DNA damages in a coordinated way. Through the combined workings of these systems, the frequency of mutations is kept in check. The result is a good balance between genetic change and stability; this balance leaves the possibility of evolution open but also protects us from the consequences of overly progressive genetic instability, such as premature aging and cancer.

DNA damage, DNA repair and cancer

Genetic mutations cannot be completely prevented, because their occurrence is a given through the chemical characteristics of our genetic substance (DNA). Consequently, it is inevitable that our cells amass mutations over the course of our lives. The older we are, the greater the risk of malignant cell transformations. If the mutation rate of our genome is additionally increased due to high-level exposure to DNA-damaging agents such as excessive sunbathing without sun protection or tobacco smoking (both of which are known risk factors for cancer), this process is accelerated. This acceleration becomes especially clear if we look at the effects of rare genetic defects in the DNA control and repair systems. Defects in these systems usually cause complex syndromes that have in common an increased incidence of cancer at a relatively young age. For example, defective functions in the ultraviolet damage repair pathway increase the risk of skin cancer even as early as in childhood.[1] Defects in genes that are responsible for repair of DNA breaks are the most common forms of inheritable breast cancer[2], and a lack of correction of DNA mismatches generated during DNA replication leads to premature development of hereditary colorectal cancer.[3]

These and many other examples show that defective DNA control and repair, which has been shown to increase the rate of genetic mutations, accelerates the development of specific types of cancer. The relationship between these genome-stabilizing functions and tumour development is not directly comparable to the effect of active tumour-promoting or tumour-inhibiting cancer genes, which are called oncogenes and tumour suppressor genes and which usually interfere directly in the control of the growth of cells.

Defects in DNA maintenance work indirectly, in that they increase genetic (and epigenetic) instability, and through this, foster the mutation of cancer genes. Defects in the DNA control and repair mechanisms, therefore, do not trigger cancer directly but instead promote the initiation and progression of tumours.

Usefulness for fighting cancer

Knowledge of the causes and mechanisms of genetic (in)stability is required for an understanding of cancer development and cancer's fundamental characteristics. Insights into the causes of genetic mutations help us to recognize environmental or lifestyle risks (such as exposure to UV light without protection, or smoking) and to minimize them through our behaviour. In addition, understanding the fundamental mechanisms makes it possible for us to develop genetic tests for the identification of heightened cancer risk. Today, for instance, family predispositions for breast and colorectal cancer can be found through preventive care before problems arise. Monitoring, preventive measures help persons affected to counteract the early development of cancer.

But this knowledge will have real usefulness for cancer treatment when the dynamic characteristics of cancer genomes become clear and predictable. This is essential, because (epi)genetic instability is the critical unknown that in the background of a tumour-promoting mutation (a mutation increasing survival and growth) is responsible for high plasticity of the cancer cells. This adaptability is a major determinant of the characteristics of a tumour, including its response and resistance to therapy. Today's treatment approaches are mainly aimed at tumour-promoting mutations, but future strategies will have to include the DNA control and repair systems, so that in addition to growth inhibition we can also control this plasticity of cancer – which its actually its Achilles

heel – and utilize it in a targeted way to its detriment. The more we know about the fundamental mechanisms and their interactions, the better we understand the genetic dynamics of a tumour with its specific defects, then the better we will be able to predict its behaviour and the better we will be able to fight cancer in a targeted and comprehensive manner. Although with our current state of knowledge we are only at the beginning of being able to do this, an increasing number of studies on medications that affect DNA repair enzymes or epigenetic regulators are showing initial promising successes in this direction.[4,5]

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5. Campbell RM, Tummino PJ. Cancer epigenetics drug discovery and development: the challenge of hitting the mark. *J Clin Invest.* 2014; 124(1): 64–69.

Prof. Primo Schär, PhD

Primo Schär studied microbiology at the University of Bern, completing a doctorate in genetics in 1991. From 1991 to 1997 he conducted molecular genetics research at the University of Bern and starting in 1993 at the Imperial Cancer Research Fund (today: Cancer Research UK) in London. He was then junior research group leader at the Institute of Molecular Cancer Research at the University of Zurich for six years. Since 2003 he has been professor of molecular genetics and research group leader at the Department of Biomedicine at the University of Basel. Prof. Schär is one of the most renowned Swiss experts on DNA repair and cancer. In 2012 he was awarded the Science Prize of the City of Basel for his outstanding work in cancer research. Since 2010 he has been a member of the Scientific Committee of the SCL and the SCR foundation.

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List of completed research projects in 2013

Aguet Michel | KFS 2674-08-2010 | CHF 234,400.–
Institut suisse de recherche expérimentale sur le cancer (ISREC), EPF de Lausanne, Lausanne
Role of BCL9/BCL9L in regulating Wnt-mediated epithelial-mesenchymal transition, stem cell traits and drug sensitivity in Wnt-activated human cancers

Andres Anne-Catherine | KLS 2825-08-2011 | CHF 114,000.–
Departement Klinische Forschung, Universität Bern, Bern
The molecular mechanisms provoking the ephrin-B2 induced deregulation of the mammary stem cell niche and leading to metastatic tumour growth

Brisken Cathrin | KFS 2462-08-2009 | CHF 331,200.–
Institut suisse de recherche expérimentale sur le cancer (ISREC), EPF de Lausanne, Lausanne
Mechanisms of action of progesterone in the human breast

Brown Steven A. | KFS 2642-08-2010 | CHF 240,100.–
Institut für Pharmakologie und Toxikologie, Universität Zürich, Zürich
The mechanism of cancer and circadian clock interactions and its usefulness in the design of therapeutic strategies

Christofori Gerhard | KLS 2535-02-2010 | CHF 283,200.–
Institut für Biochemie und Genetik, Departement Biomedizin, Universität Basel, Basel
The functional role of the transcription factors Dlx2 and Lhx2 in epithelial-mesenchymal transition (EMT) and in malignant tumour progression

Constam Daniel | KFS 2487-08-2009 | CHF 307,600.–
Institut suisse de recherche expérimentale sur le cancer (ISREC), EPF de Lausanne, Lausanne
Role of activin signalling in metastatic melanoma

Dufour Jean-François | KFS 2541-02-2010 | CHF 202,200.–
Universitätsklinik für Viszerale Chirurgie und Medizin, Universität Bern, Bern
Hepatocarcinogenic roles of mTOR, raptor and rapamycins in absence of Pten

Gönczy Pierre | KLS 2584-02-2010 | CHF 197,000.–
Institut suisse de recherche expérimentale sur le cancer (ISREC), EPF de Lausanne, Lausanne
Mechanisms of centrosome duplication: from model organism towards therapeutic opportunities

Grassi Fabio | KFS 2445-08-2009 | CHF 144,000.–
Istituto di ricerca in biomedicina (IRB), Bellinzona
Purinergic signalling in the pathophysiology of central nervous system infiltration in T-cell leukaemia

Hall Jonathan | KFS 2648-08-2010 | CHF 226,000.–
Institut für Pharmazeutische Wissenschaften, ETH Zürich, Zürich
Targeting pre-let-7 biogenesis in cancer

Hynes Nancy | KFS 2743-02-2011 | CHF 205,400.–
Friedrich Miescher Institut für biomedizinische Forschung (FMI), Basel
Role of the bone marrow niche in breast cancer metastasis and therapy response

Krek Wilhelm | KFS 2690-08-2010 | CHF 226,000.–
Institut für Zellbiologie, ETH Zürich, Zürich
Roles of the URI oncoprotein in B-RAF signalling and melanoma cancer cell proliferation

Meraldi Patrick | KFS 2707-08-2010 | CHF 226,000.–
Centre médical universitaire (CMU), Université de Genève, Genève
How does overexpression of the Aurora-A oncogene override the spindle checkpoint?

Michielin Olivier | KFS 2555-02-2010 | CHF 304,500.–
Département d'oncologie, Centre hospitalier universitaire vaudois (CHUV), Lausanne
Rational design of anti-MART-1 TCR sequences for adoptive transfer immunotherapies

Ochsenbein Adrian F. | KLS 2342-02-2009 | CHF 320,450.–
Universitätsklinik für Medizinische Onkologie, Inselspital, Universitätsspital Bern, Bern
Immunogenicity of chronic myeloid leukaemia stem cells

Pertz Olivier | KFS 2485-08-2009 | CHF 333,000.–
Institut für Biochemie und Genetik, Departement Biomedizin, Universität Basel, Basel
A Slit/Robo signalling pathway regulating contact-mediated repulsion during cell migration: implications of its deregulation for the acquisition of an invasive phenotype during breast cancer

Petrova Tatiana | KLS 2570-02-2010 | CHF 198,300.–
Centre pluridisciplinaire d'oncologie (CePO), Centre hospitalier universitaire vaudois (CHUV) et Université de Lausanne, Epalinges
Lymphatic endothelial calcineurin/NFAT signalling in tumour lymphangiogenesis and metastasis

Pruschy Martin | KFS 2551-02-2010 | CHF 303,700.–
Klinik für Radio-Onkologie, Universitätsspital Zürich, Zürich
Differential response to proton versus photon radiotherapy: biological implications for new indications and combined treatment concepts

Radtke Freddy | KFS 2272-08-2008 | CHF 191,800.–
Institut suisse de recherche expérimentale sur le cancer (ISREC), EPF de Lausanne, Lausanne
Candidate genes implicated in melanoma – genetic and developmental in vivo analysis

Ruiz i Altaba Ariel | KFS 2359-02-2009 | CHF 339,500.–
Département de génétique médicale et de développement, Faculté de médecine, Université de Genève, Genève
Role and prevalence of hedgehog signalling in human colorectal cancer

Schäfer Beat W. | KLS 2784-02-2011 | CHF 217,500.–
Abteilung Onkologie, Kinderspital Zürich, Universitäts-Kinderkliniken, Zürich
Preclinical and mechanistic evaluation of FGFR4 signalling in rhabdomyosarcoma

Schär Primo | KFS 2585-02-2010 | CHF 237,500.–
Institut für Biochemie und Genetik, Departement Biomedizin, Universität Basel, Basel
DNA repair, epigenetic stability, and CpG island hypermethylation in colorectal tumourigenesis

Schorderet Daniel | KFS 2565-02-2010 | CHF 197,000.–
Institut de recherche en ophtalmologie (IRO), Sion
Retinoblastoma: understanding its development for better treatment

Schwaller Jürg | KFS 2778-02-2011 | CHF 238,500.–
Departement Biomedizin, Universitätsspital Basel, Basel
Dissecting the cellular origin and molecular targets in MLL acute leukaemia

Thome-Miazza Margot | KFS 2561-02-2010 | CHF 198,300.–
Département de biochimie, Université de Lausanne, Epalinges
Analysis of the role of the protease MALT1 in human lymphomas

Widmann Christian | KFS 2543-02-2010 | CHF 205,300.–
Département de physiologie, Université de Lausanne, Lausanne
The 317–326 sequence of RasGAP as potential anti-metastatic agent

Wymann Matthias P. | KFS 2680-08-2010 | CHF 343,000.–
Institut für Biochemie und Genetik, Departement Biomedizin, Universität Basel, Basel
Identification and modulation of targets to reprogramme glioblastoma cancer stem cells

Zavolan Mihaela | KFS 2477-08-2009 | CHF 303,000.–
Departement Biozentrum, Universität Basel, Basel
Identification of cancer-related targets of individual members of the miR-17-92 cluster of miRNAs

Presentation of completed research projects in 2013

Aguet Michel | **Role of BCL9/BCL9L in regulating Wnt-mediated epithelial-mesenchymal transition, stem cell traits and drug sensitivity in Wnt-activated human cancers** (KFS 2674-08-2010)

The concept of cancer stem cells (CSCs) has stimulated new directions for addressing the problem of cancer treatment. CSCs are increasingly viewed as responsible, at least in part, for the emergence of resistance to therapy and tumour recurrence. Therapy-refractory tumour cells from a variety of solid tumours have been reported to exhibit stem cell-related traits and may represent CSC-enriched tumour cell populations selected under therapeutic constraint. Targeting CSCs has therefore emerged as a tempting new therapeutic strategy.

We recently described a mouse model of colon adenocarcinoma in which a signalling branch of the Wnt pathway (BCL9) was critically involved in CSC maintenance. We showed that inactivating this branch resulted in virtual loss of stemness and other malignancy associated traits. This project aimed at validating these findings in other models, including human cancer cell lines. We were able to identify a human colon cancer cell line based upon expression of intestinal stem cell markers, which appeared to consist of heterogeneous subpopulations of stem cell-like as well as more differentiated cells, pointing to a spontaneously occurring differentiation cascade. Preliminary findings suggest that the same Wnt signalling branch is involved in regulating this equilibrium and that more differentiated cells lose stemness as well as associated malignancy traits.

The aim was to explore to what extent pharmacological inhibition of BCL9 proteins may be of benefit in the context of a combination therapy to reduce the CSC pool and the risk of tumour recurrence.

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Andres Anne-Catherine | **The molecular mechanisms provoking the ephrin-B2 induced deregulation of the mammary stem cell niche and leading to metastatic tumour growth** (KLS 2825-08-2011)

Stem and progenitor cells are thought to represent the origin of carcinogenesis and to be responsible for metastatic tumour growth. Thus, the elaboration of efficient treatment strategies depends at least in part upon a profound understanding of the mechanisms controlling stem cell development. We showed previously that deregulated expression of the receptor EphB4 and its ligand ephrin-B2 in the mammary epithelium alters the stem cell niche and thereby contributes to metastatic tumour growth.

In this project, we investigated whether the abnormal behaviour of the stem cells originates from the stem cells themselves or is the consequence of abnormal stimulation by the neighbouring cells constituting their niche. Moreover, we aimed to identify the molecular pathway transmitting the EphB4-ephrin-B2 emitted signals. To these ends, we isolated the mammary epithelial cells of transgenic mice exhibiting deregulated expression of EphB4 or ephrin-B2 and separated these cells into four distinct cell populations: luminal and basal progenitors, bi-potent progenitors, and the stem cells. From each of these cell populations we determined the gene expression profile and compared these profiles to those of normal mammary epithelial cells.

These experiments revealed that components of the Wnt signalling pathway and the oestrogen receptor are predominantly affected by the aberrant EphB4 or ephrin-B2 expression. The oestrogen receptor is the main inducer of mammary epithelial proliferation in the adult, whereas signalling by Wnt growth factors is involved in a variety of morphogenic processes such as determination of tissue boundaries and pattern formation. Interestingly, the main discrepancies were found in the bi-potent progenitor cells and the stem cell population, which both do not express the transgenes.

These results demonstrate that EphB4 and ephrin-B2 exert their effect indirectly by activating the Wnt and oestrogen signalling cascade. Thus, our project has led to the identification of a particular aspect of the control mechanisms ensuring the homeostasis of the stem cell niche that might be a suitable target for stem cell specific therapeutic intervention.

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Brisken Cathrin | **Mechanisms of action of progesterone in the human breast** (KFS 2462-08-2009)

Sex hormones are known culprits in breast cancer. For example, women undergoing combined hormone replacement therapy with artificial progesterone mimics (called progestins) and oestrogen have an increased risk of getting breast cancer.Unfortunately, it is difficult to study the effects of these hormones on normal breasts. Fresh breast cells grown in the lab quickly lose their hormone receptors for reasons that we still do not understand. Mouse models can be useful, but mouse mammary glands are different from human mammary glands, and the animals tend to get unique types of breast cancers that are not seen in humans. We studied fresh pieces of breast tissue taken from women (with no previous history of breast cancer) undergoing breast reduction surgery and developed a tissue microstructure technique that preserves breast cells' natural environment in the lab.

We found that progesterone boosts cell growth in normal breasts. Cells in breast milk ducts start to produce large amounts of a secreted protein called RANKL in response to progesterone. RANKL seems to be the loudspeaker that progesterone uses to command breast cells to proliferate. If these cells are repeatedly stimulated by progesterone, breast cancer risk may increase. Inhibiting progesterone or RANKL with denosumab, a drug already used to treat bone diseases, could potentially benefit women under 50 who are at high-risk of developing breast cancer.

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Brown Steven A. | **The mechanism of cancer and circadian clock interactions and its usefulness in the design of therapeutic strategies** (KFS 2642-08-2010)

The circadian clock and the cell cycle are two autonomous regulatory cascades that control cellular physiology, metabolism and division. Dysfunction of either can lead to cancer. In our project, we sought to understand the mechanisms linking these two cascades, and how exploiting these connections might lead to improved therapeutic strategies.

Aims of the study
First, we sought to understand whether primary human tumours show the wide range of circadian function shown in tumour cell lines, using glioblastoma multiforme as a model. Second, we wished to understand how the presence or absence of a functional circadian clock could change tumour growth and physiology.

Methods
With the help of virally delivered bioluminescent reporters, we examined cell-autonomous circadian rhythms of gene expression in cells from different primary tumours. In a second step, we injected clock-containing and similar clock-less tumours expressing the same bioluminescent reporters into mice and examined both tumour growth rates and circadian cell division *in vivo*.

Results
In vitro, we showed that some human tumour cells possess perfectly functional circadian clocks and others no clock at all, even in tumours of the same grade. Surprisingly, in an experimental mouse model no differences in tumour growth rate were observed between clock-containing and clock-less tumours, and both types showed circadian cell division *in vivo*. Therefore, the host animal's circadian clock gates tumour cell division systemically, even in the absence of local clock function.

Potential relevance for patients
If tumour growth is gated by host circadian function, then reduction in tumour growth rates might be achieved both by supporting host circadian function and by optimized timing of chemo- and radiotherapy.

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Christofori Gerhard | **The functional role of the transcription factors Dlx2 and Lhx2 in epithelial-mesenchymal transition (EMT) and in malignant tumour progression** (KLS 2535-02-2010)

Most cancer deaths are due to the systemic dissemination of cancer cells and the formation of secondary tumours (metastasis) in distant organs. The majority of cancers originate from epithelial tissues. To leave the primary tumour and to invade into the surrounding tissue, tumour cells dissolve their cell-cell contacts and adjust to a more transient, migratory and invasive mode. This temporary and reversible phenomenon is known as an epithelial-to-mesenchymal transition (EMT), a multistage process that involves a dramatic reprogramming of cancer cells and leads to metastasizing cells with stem cell-like capabilities.

We identified an increased expression of the transcription factors Dlx2 and Lhx2 during EMT. Gain and loss of function experiments have delineated the regulatory functions of Dlx2 and Lhx2 during EMT *in vitro* and during metastasis formation in mouse models of cancer *in vivo*. Employing chromatin-immunoprecipitation experiments, we identified direct targets of Dlx2 and Lhx2 transcriptional control and analysed the functional contribution of some of these target genes to EMT and malignant tumour progression. Finally, we assessed whether the gene expression signatures identified here may provide prognostic tools for the prediction of clinical outcome in patients.

We found that Dlx2 exerts critical functions during malignant tumour progression by counteracting TGFβ-induced cell cycle arrest and apoptosis by at least two molecular mechanisms: Dlx2 acts as a transcriptional repressor of TGFβ receptor II expression and thus overcomes TGFβ-mediated cell cycle arrest. On the other hand, Dlx2 induces the expression of the epidermal growth factor (EGF) family member Betacellulin, which promotes cell survival by stimulating EGF receptor signalling. Finally, Dlx2 expression supports experimental tumour growth

Fotogramm / Erle, 2011

and metastasis and correlates with tumour malignancy in a variety of human cancer types. For Lhx2 we found that it promotes vessel maturation, primary tumour growth, tumour cell intravasation and metastasis by inducing the expression and secretion of platelet-derived growth factor (PDGF)-B by tumour cells. The data indicate that Lhx2 exerts a dual role in malignant tumour progression by provoking autocrine PDGF-B signalling required for metastatic dissemination and paracrine PDGF-B signalling to support blood vessel functionality and primary tumour growth.

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Constam Daniel | **Role of activin signalling in metastatic melanoma** (KFS 2487-08-2009)

Aim of the study

Melanoma, the deadliest type of skin cancer, has a poor prognosis once it forms metastases. What triggers metastatic spread is not well understood. Activin and related secreted growth factors that regulate the development of stem cells in healthy tissues are also found in several cancers including melanoma, especially during the progression towards metastatic growth. We therefore asked whether such factors promote melanoma progression, and by what mechanism(s).

Methodology

To address this question, we assessed the effects of activin and the consequences of inhibiting activin by genetic approaches in mice that received grafts of melanoma cells. We also tested whether activin influences the tumour cells directly or indirectly by altering their microenvironment in the host tissue.

Results
In immunodeficient mice, we found that grafts of human melanoma cell lines formed metastases irrespective of the presence or absence of activin but that tumour-derived activin was responsible for a dramatic loss of body weight, consistent with its known inhibitory effect on muscle stem cells. A similar weight loss was induced by activin in mice with a normal immune system that received mouse melanoma cells. However, in this context, activin in addition dramatically accelerated the growth of primary tumours and of lung metastases, suggesting that its tumourigenic effect consists largely in suppressing an anti-tumour immune response. Concurring with this conclusion, direct effects of activin on melanoma cells themselves varied among cell lines and were not sufficient to promote tumourigenesis.

Significance
Metastatic growth and tumour-induced muscle loss are the major cause of cancer deaths, but neither process is sufficiently understood at the molecular level to design effective therapies. Another major challenge is that an abnormal high frequency of gene mutations enables cancer cells to rapidly develop drug resistance. Our new findings suggest that existing or future activin inhibitors will likely benefit at least a subset of melanoma patients by blocking tumour-induced immune evasion. Moreover, since activin primarily acts on the host immune system rather than on the genetically unstable cancer cells, resistance to such drugs is less likely to develop.

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Gönczy Pierre | **Mechanisms of centrosome duplication: from model organism towards therapeutic opportunities** (KLS 2584-02-2010)

We focused the bulk of our study on the analysis of two proteins, HsSAS-6 and CPAP, which are necessary for centrosome duplication, a process that is essential for cell proliferation and that is often aberrant in cancer cells.

Aims of the study
The centrosome contains two centrioles and is the organelle that ensures microtubule organization in animal cells. Centrosome duplication occurs only in proliferating cells and is necessary for correct cell division. Cancer cells often exhibit aberrations in the number or structure of centrosomes. Therefore, centrosome duplication offers therapeutic opportunities in the fight against cancer.

Methods
We combined the advantages of two experimental systems, the nematode C elegans and human cells in culture, to obtain novel information regarding the mechanisms of centrosome duplication, in particular through analysis of the HsSAS-6 and CPAP proteins.

Results of the study
In C. elegans, we have begun to study the consequences of abnormal centriole number or structure in a stem cell lineage. Moreover, we analysed in detail the way in which HsSAS-6 and CPAP contribute to the formation of centrioles in human cells in culture. Further, using proteomic methods, we identified proteins that are associated with HsSAS-6 and that may modulate its function in normal cells, as well as in tumour cells. In the long term, we expect this research to lead to the identification of new drugs that target preferentially proliferating cells harbouring centrosome aberrations, as is characteristic of numerous cancer cells.

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Grassi Fabio | **Purinergic signalling in the pathophysiology of central nervous system infiltration in T-cell leukaemia** (KFS 2445-08-2009)

Adenosine-triphosphate (ATP) is usually confined inside the cell, where it constitutes the source of chemical energy for cellular functions. ATP is also released by cells as a signalling molecule. In T-cells extracellular ATP regulates T-cell proliferation and activity but can also promote cell death via purinergic P2 receptors.

Aim of the study
The aim of this study was to address whether pharmacological inhibition of P2 receptors might be useful in T-acute lymphoblastic leukaemia (T-ALL) therapy and ameliorate central nervous system infiltration, a dramatic complication of T-ALL.

Method and procedure
We tested *in vitro* the effect of periodate-oxidized ATP (oATP), a P2 receptors inhibitor, on the proliferation of T-ALL cells from mice with leukaemia. Among the leukaemic cell population, only a small subset of cancer stem cells can initiate, regenerate and maintain leukaemia after transplantation. The haematopoietic niche in the bone marrow constitutes a reservoir of T-ALL stem cells. We addressed whether purinergic antagonism might control haematopoietic stem cells pool size and self-renewal in the bone marrow. Finally, we tested treatment *in vivo* with oATP in immunodeficient mice transplanted with T-ALL cells.

Results of the study
The treatment with oATP prominently inhibited expansion of T-ALL cells *in vitro*, thus suggesting that ATP contributes to the expansion of T-ALL cells via P2 receptors. We showed that oATP decreased the number of proliferating cells in the haematopoietic niche of the bone marrow (BM), which is exploited by T-ALL stem cells for constant regeneration, indicating that P2 activation contributes to leukaemogenesis. Since P2 stimulation by ATP can in turn induce ATP release, self-perpetuating release of ATP by T-ALL stem cells might play an important role in controlling their activity and constant generation of circulating

leukaemic cells. *In vivo* treatment with oATP revealed the importance of BM niche as a site of T-ALL proliferation, as a prelude to central nervous system infiltration by leukaemia.

Potential benefits for patients
This research project revealed the importance of ATP in regulating leukaemogenic potential of T-ALL cells residing in the BM and of BM as a prominent site for progression to the neuropathological form of the disease.

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Hall Jonathan | **Targeting pre-let-7 biogenesis in cancer** (KFS 2648-08-2010)

Many human cancers exhibit dysregulation of microRNA expression, in which they are non-functional or overexpressed. A prominent example is the let-7 family, in which let-7 prevents normal cells from becoming tumourigenic. In several cancers levels of let-7 are very low. This is due to the RNA-binding protein Lin28, which binds to the precursor of let-7, preventing its correct processing. New studies have shown also that the Lin28/let-7 plays an important role in maintenance of cancer stem cells. In the previous project, we synthesized short antisense oligonucleotides that bind to the let-7 precursor and protect it from degradation by Lin28. This leads to increased levels of let-7 in cells and inhibition of cancer cell growth.

One goal of this project was to improve the properties of the antisense oligonucleotides through chemical modification. This should lead to a stronger effect on the precursor and will be examined in mouse cancer models. The results of the study have provided new insights into the mechanisms of anti-microRNA antisense oligonucleotides in living models of cancer.

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Hynes Nancy | **Role of the bone marrow niche in breast cancer metastasis and therapy response** (KFS 2743-02-2011)

Metastatic breast cancer, the major cause of breast cancer deaths, is currently not treatable. To uncover new approaches to block metastasis, we established mammary carcinoma models with bone marrow (BM) tropism using tumour cell lines representing common breast cancer subtypes. To characterize BM specific changes, metastatic cancer cells were isolated, and gene expression profiling was carried out and compared to patterns obtained from cancer cells isolated from primary mammary tumours. A number of differentially expressed genes were uncovered. For example, in bone metastases, the expression of ID1 was significantly increased compared to its level in tumour cells growing in the mammary gland. ID (inhibitor of differentiation/DNA binding) is a family of helix-loop-helix proteins that do not possess a DNA binding domain but function as dominant-negative regulators of basic helix-loop-helix transcription factors that regulate the differentiation programme of multiple cell lineages. Moreover, ID1 expression correlates with less differentiated phenotypes, high malignant potential and poor clinical outcome in breast cancer. Thus, it is possible that ID1 is required for the establishment of bone metastases. We are testing this hypothesis now, by introducing tumour cells with a specific knockdown of ID1 into the bone and examining their ability to form metastases.

To complement the analyses of tumour cells growing in the bone vs. the mammary gland, we also asked how subpopulations of BM environmental cells are affected by the presence of cancer cells. For this, BM stromal cell subsets of endothelial, osteoblastic and mesenchymal cells were FACS purified from tumour-free vs. bone tumour-bearing mice and subjected to transcriptome analyses. A number of genes that were significantly up- or downregulated in response to the presence of tumour cells were uncovered. An ingenuity pathway analysis also allowed us to delineate the signalling pathways specific for the individual subpopulations of stromal cells that are altered in the presence of bone metastases. These analyses provide us with new opportunities to test specific inhibitors, a project that is ongoing in the lab.

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Meraldi Patrick | **How does overexpression of the Aurora-A oncogene override the spindle checkpoint?** (KFS 2707-08-2010)

Amplification or overexpression of the Aurora-A gene is frequently observed in human cancers and has been associated in human patients with resistance to taxanes, one of the major classes of anti-cancer agents. Aurora-A is a protein kinase that regulates the entry into mitosis and controls the formation of the bipolar spindle, the structure that separates the sister chromatids during cell division. However, the pathological effects of Aurora-A overexpression are less well understood. The leading hypothesis is that elevated Aurora-A kinase activity impairs the spindle checkpoint, a surveillance mechanism that prevents mitotic exit in the presence of erroneous attachment of chromosomes to the mitotic spindle. Importantly, Aurora-A kinase inhibitors are a new class of drugs that are currently being tested as anti-cancer agents in clinical trials.

Our aim was to understand how overexpression of the protein kinase Aurora-A affects the spindle checkpoint at the molecular level. Our results confirm previous studies showing that Aurora-A overexpression leads to errors in chromosome segregation during cell division. However, to our surprise we found that overexpression of Aurora-A

impairs the fidelity of cell division in a kinase-independent manner and that it does not disrupt the spindle checkpoint. Instead, Aurora-A overexpression leads to chromosome bridges, fine threads to DNA that link the two dividing chromosome masses as cells divide. These chromosome bridges can impair cell division, leading to cells with the double amount of chromosomes. This suggests a new mechanism by which Aurora-A affects dividing cells.

Our current aim is to understand how the overexpression of Aurora-A results in such DNA bridges. Finally, our data suggest that Aurora-A kinase inhibitors might not be able to target cells overexpressing Aurora-A, since Aurora-A overexpression seems to affect mitosis in a kinase-independent manner.

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Michielin Olivier | **Rational design of anti-MART-1 TCR sequences for adoptive transfer immunotherapies** (KFS 2555-02-2010)

The adoptive cell transfer immunotherapy against cancer relies on the ability of the killer T-cells of the immune system to recognize and specifically destroy cancer cells. This recognition is achieved thanks to a receptor called T-cell receptor (TCR), which recognizes specifically a cancer antigen presented at the cancer cell surface by the major histocompatibility complex (MHC). The recognition of the cancer antigen by the TCR starts a cascade of biochemical events that will finally destroy the cancer cell. The adoptive cell transfer immunotherapy consists in extracting killer cells from the patient that are specific for the disease, expanding them ex vivo, and re-injecting them in the patient to create an efficient immune response against the tumour.

The objective of this project was to optimize the structure of a TCR binding specifically to melanoma cancer cells using rational computer-aided protein engineering, to optimize its binding to tumour cells and thus their killing. We have developed a new method based on the 3D structure of the TCR/antigen complex and free energy simulation, with which we could modify rationally the sequence of a TCR targeting a cancer antigen called NY-ESO-1. We obtained a 150-fold increase in the TCR potency for the binding to melanoma cancer cells. We showed that by engineering *in vitro* the patient T-cells to express these modified TCRs, it is possible to dramatically increase the immune response against melanoma cells.

In this project, we applied this method to rationally modify a TCR targeting another very common melanoma antigen, i. e. Melan-A. We have chosen to rationally optimize a Melan-A-specific Mel5 TCR, whose structure in a complex with the Melan-A antigen presented by the HLA-A*0201 MHC was available. We designed 26 mutations possibly enhancing the binding to this antigen. These mutants were produced and tested for binding in titration ELISA as compared to the wild-type (natural) TCR. 19 mutants out of 26 (73 %) were found more active than the wild-type TCR. Thanks to this success, we now have at our disposal a pool of optimized TCR recognizing specifically several melanoma antigens, which could be of major importance for the design of enhanced adoptive cell transfer immunotherapy.

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Ochsenbein Adrian F. | **Immunogenicity of chronic myeloid leukaemia stem cells** (KLS 2342-02-2009)

Chronic myeloid leukaemia (CML) is a clonal myeloproliferative disease that originates from a transformed haematopoietic stem cell or progenitor cell. This results in leukaemia stem cells (LSCs). LSCs are resistant to most of the current treatments including chemotherapy, radiotherapy and tyrosine kinase inhibitors. LSCs are therefore the main reason for relapse after treatment, and cure of the disease implies the elimination of LSCs. We established a murine CML model by transducing bone marrow cells with the oncogene BCR/ABL. In this model, leukaemia-specific cytotoxic T-lymphocytes (CTLs) are activated and contribute to the elimination of more differentiated leukaemia cells. Surprisingly, specific CTLs did not eliminate LSCs but in contrast increased their numbers. We identified two mechanisms by which CTLs contribute to the proliferation and expansion of LSCs.

First, we analysed the role of the CD27 signal transduction in leukaemogenesis. CD27 is a co-stimulatory molecule that induces T-cell expansion and memory generation. We documented that CD27 is expressed on LSCs and that CD27 signalling increases LSCs proliferation and differentiation into more mature granulocytes. The ligand of CD27 (CD70) is exclusively expressed on activated lymphocytes and on mature dendritic cells. Therefore, the activated immune system contributes to leukaemia progression. Importantly, blocking the CD27/CD70 interaction by treatment with monoclonal antibodies eliminated LSCs and prolonged survival.

In a second study we focused on the inflammatory cytokine interferon-gamma (IFN). Activated cytotoxic T-lymphocytes produce large amounts of IFN when transferred to a CML-bearing mouse. IFN induced the proliferation of CML stem cells and increased their numbers. Therefore, immunotherapy with CTLs is the most efficient in a setting with a reduced leukaemia load after chemotherapy or in combination with a strategy to block IFN . Knowledge of these molecular pathways can be used to improve immunotherapy against LSCs.

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Pertz Olivier | **A Slit/Robo signalling pathway regulating contact-mediated repulsion during cell migration: implications of its deregulation for the acquisition of an invasive phenotype during breast cancer** (KFS 2485-08-2009)

In healthy tissue, individual cells are kept in the right order through constant interaction with neighbouring cells. This process involves sampling of adjacent cells and sensing of repulsive cues that suppress cell motility. During the metastatic switch, cancer cells acquire the ability to move out and to squeeze between surrounding cell layers, finally spreading through the body and colonizing distinct organs. Thus, cell sensing may serve as an important early mechanism to impede the invasive phenotype. The aim of this project was to apply a gene inactivation approach to identify signalling pathways that generate and/or sense repulsive signals.

In this study we identified the Slit-Robo-srGAP pathway as a central regulator of cell repulsion. This pathway consists of the extracellular activator molecule Slit, which binds to its receptor Robo that is present in the plasma membrane. This interaction triggers the activation of the receptor and subsequent recruitment and activation of srGAP proteins by Robo. Active srGAP molecules induce the reorganization of the cytoskeleton, which leads to cell repulsion.

Downregulation of Slit, Robo and srGAP protein levels in cells leads to prolonged cell-cell contact duration and increased cell-cell overlap. Moreover, those cells protrude very efficiently and are able to invade neighbour cells. We were also able to show that Slit and srGAP proteins localize to the front edge of migrating cells. This means that migrating cells are already prepared to adequately respond to collisions encountered on their way. This collision detector functions as a "bumper" to prevent unintended cell movements. This may be an important mechanism in tumour metastasis. Indeed, inactivation of the Slit-Robo pathway has been reported in human cancers, although the precise mechanisms of action are not yet fully understood. Thus, understanding the molecular mechanisms underlying metastasis will be crucial for successful cancer therapy.

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Pruschy Martin | **Differential response to proton versus photon radiotherapy: biological implications for new indications and combined treatment concepts** (KFS 2551-02-2010)

There is presently a widening gap between the rapid introduction of proton therapy in clinical practice worldwide and the introduction of new proton treatment concepts with an apparent lack of solid radiobiological evidence and data to support the expansion of new clinical indications, particularly when combined with other treatment modalities.

In collaboration with the Paul Scherrer Institute (PSI)-based Centre for Proton Therapy, we investigated underlying mechanisms for proton radiation-induced cell killing. The major questions arise from the observed (in the absence of systematic molecular and cellular investigations) differential biological effectiveness of clinically relevant proton versus clinically relevant photon irradiation.

In genetically defined cellular systems we analysed: (1) underlying biological and molecular parameters that may contribute to the relative biological effectiveness, (2) a differential mode of cell death in response to the different types of radiation, and (3) the treatment responses to combined treatment modalities with currently relevant anti-signalling agents and the two types of radiation. We have identified that a deficiency in one of the major DNA damage repair machineries renders mammalian cells more sensitive to proton versus photon irradiation.

This project will be continued, and the anticipated results will further promote and improve proton radiotherapy from the biological perspectives.

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Radtke Freddy | **Candidate genes implicated in melanoma – genetic and developmental *in vivo* analysis** (KFS 2272-08-2008)

Melanoma derives from melanocytes and is currently one of the most aggressive forms of skin cancer. Melanocytes are pigment cells found in skin, hair, inner ear and eye. The significance of malignant melanoma incidence has been increasing in recent years, with an annual growth of over 2 %. The fatal outcome of melanoma is mostly due to metastasis. Although most of the frequently mutated genes in melanoma are known, treatment for metastatic melanoma remains a challenge. A better understanding of the biological mechanisms regulating melanoma development and progression is therefore critical for developing effective therapeutic interventions against advanced melanoma.

Aim of the study
Here we addressed the role of two candidate pathways (Notch and c-Myc) for their role during normal melanocyte development as well as in the context of malignant melanoma.

Methods
We used and combined different genetically engineered mouse models in which Notch receptors or the c-Myc gene can specifically be inactivated or overexpressed in murine pigment cells and melanomas. Moreover, we correlated c-Myc protein levels in primary and metastatic murine and patient-derived melanoma samples with disease aggressiveness.

Results
Our experiments showed that both Notch signalling and c-Myc are essential for melanocyte development. Moreover, we established the functional significance of the Notch cascade in pigmented eye structures. Mice with loss- and gain-of-function studies for Notch developed ocular hypotony and ocular hypertension, respectively, mimicking the human diseases phthisis bulbi and closed angle glaucoma. Genetic studies of c-Myc in a murine melanoma model established the essential role of c-Myc for melanoma development and for melanoma maintenance. c-Myc protein levels were found to be lower in primary melanoma compared to metastatic lesions both in mice and in human tumour samples, which correlated with the aggressiveness of the tumour. Moreover, c-Myc positive melanoma cells have a higher tumour initiation potential compared to c-Myc negative cells.

Relevance
Our studies regarding pigmented eye structures provide novel insights on the role of Notch signalling in the eye, and the genetic models developed represent robust tools to study the aetiology, pathology and treatment of diseases related to aberrant intraocular pressure, such as phthisi bulbi and closed angle glaucoma. Our studies on melanoma revealed important roles for c-Myc as a potential prognostic marker for progression and aggressiveness of murine and human melanoma.

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Ruiz i Altaba Ariel | **Role and prevalence of hedgehog signalling in human colorectal cancer**
(KFS 2359-02-2009)

In this project we addressed the unresolved question of the role of this important signalling pathway in colon cancer. In tumours, as in normal tissues, cells communicate with each other, and understanding how they do it is of utmost importance for the fate of the tissues and, in our case, the cancers, but also for designing rational and targeted therapies. There are only a handful of different communication pathways that are used over and over but in different modes, strengths and contexts. In our case, we focused on the HEDGEHOG (HH)-GLI pathway, which is important for the development of the embryo, the construction of many tissues and their maintenance in adulthood, and for cancers of many types.

In terms of colon cancer, before our studies it was proposed that the HH-GLI pathway was not important. Our findings have proven otherwise. We show that its requirement for tumour growth and metastasis is widespread. Importantly, we have used patient samples obtained from our surgeon collaborators and have shown *in vitro* and in mouse grafts (the closest to a patient that we can manage for experimentation in the laboratory) that blocking the activity of this signalling pathway leads to tumour regression, prevents recurrence, and leads to tumour cell death. Importantly, we also show that cancer stem cells, the cells in the tumour that appear responsible for maintaining tumour growth and expanding it locally and distally in metastasis, also show a dependence on this pathway.

Our results thus prove the role of the HH-GLI pathway in human colon cancers and their stem cells and thus open the possibility for their treatment with HH-GLI blockers. Since several companies have developed and are developing such blockers, our data set the stage for rational, well-designed clinical trials.

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Schäfer Beat W. | **Preclinical and mechanistic evaluation of FGFR4 signalling in rhabdomyosarcoma**
(KLS 2784-02-2011)

The FGFR4 is a key receptor transmitting signals from outside to the cell nucleus, which is strongly activated in the paediatric tumour alveolar rhabdomyosarcoma (aRMS). FGFR4 downstream signalling is mediated by a range of distinct signalling pathways that can influence the efficacy of current or future therapies. In this project, we aimed to identify and characterize FGFR4 signals so as to better understand therapy resistance and to find promising, more effective therapies in the future.

Aim of the study
Characterization of FGFR4 signalling under established and experimental therapies in aRMS cells.

Methods
Eight aRMS cell lines were treated with different established and experimental drugs in presence of bFGF to activate FGFR signalling. Activation of programmed cell death was then measured using common assays. Differences between the cell lines were studied on the molecular level and validated in a large cohort of 45 aRMS tumours by gene expression analysis and immunohistochemical stainings.

Results
bFGF blocked the induction of cell death in a subgroup of cell lines, with no effect on the other cells. The two subgroups differed in the molecular sensor involved in activation of cell death under our treatment conditions. In cells where cell death was blocked, this sensor is the protein Bim or Bad, whereas in the other cells it is the protein Bmf. FGFR4 signalling is able to inactivate Bim by a combination of mechanisms, but Bmf is not affected. The two subtypes of cells are also detectable in aRMS tumours. They are present in different ratios in different tumours, with some tumours being composed mainly of cells from one or the other subtype and other tumours containing a mixture of the two cell types. Specific inhibition of the FGFR4 makes it possible to overcome the block of cell death in presence of bFGF.

Relevance
Our results show for the first time that two physiologically different tumour cell types are present in aRMS. This implies that novel therapeutic approaches have to be evaluated for effectiveness in both of these. The inhibitory effect of FGFR4 signalling on tumour cell death during therapies might be overcome by using a combination including FGFR4 inhibitors.

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Schär Primo | **DNA repair, epigenetic stability, and CpG island hypermethylation in colorectal tumourigenesis** (KFS 2585-02-2010)

Cancer arises through genetic and epigenetic changes that transform normal cells into malignant cells. Epigenetic changes concern small chemical chromatin modifications that act as flags to instruct cell type-specific gene expression. A prominent epigenetic modification is the methylation of cytosine in DNA, which, established in tissue-specific patterns, is disturbed in many cancers. Cancer cells can acquire a "methylator phenotype" characterized by widespread aberrant hypermethylation of gene promoters, implicating an as yet unidentified malfunction in the DNA methylation system. We previously discovered a role for thymine-DNA glycosylase (TDG)-mediated DNA excision repair in the maintenance of promoter hypomethylation. This project examined whether malfunction of this system can account for aberrant promoter methylation associated with colorectal carcinogenesis.

Aims of the study
Our objectives were to profile DNA methylation patterns of the methylator phenotype in colorectal cancer (CRC), to correlate the expression of TDG and associated demethylation proteins with the methylator phenotype, and to determine the contribution of TDG-dependent processes to the maintenance of methylation stability at gene promoters.

Methods
Genome-wide approaches were combined with bioinformatic analyses for DNA methylation profiling of the colonic mucosa, CRCs and CRC cell lines. Expression of demethylation factors in these tissues was assessed at the mRNA and protein levels. Association of TDG and TET proteins with relevant gene promoters was examined by chromatin immunoprecipitation.

Results
We were able to discriminate age-dependent and cancer-associated DNA methylation changes at a genomic level and, thereby, to identify > 800 loci, the methylation status of which may predict the risk of developing CRC. Importantly, we found that methylator and non-methylator cancers differ primarily in levels rather than the genomic distribution (targets) of aberrant DNA methylation, and we showed that the TET-TDG demethylation capacity is downregulated in methylator cancers, thus explaining gene promoter hypermethylation by reduced demethylation.

Relevance
The study provides unprecedented insight into the contribution of DNA methylation instability to colorectal carcinogenesis. It identifies a comprehensive set of genomic loci as potent biomarkers for the detection of carcinogenesis in the aging colonic mucosa, and it uncovers a molecular mechanism explaining the hypermethylation phenotype of colorectal cancers.

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Schorderet Daniel | **Retinoblastoma: understanding its development for better treatment** (KFS 2565-02-2010)

Retinoblastoma is a malignant tumour of the developing retina that manifests in early childhood. Retinoblastoma development requires the loss of both RB1 alleles, but accumulation of additional genomic/epigenetic changes are involved in the tumour progression. Highly proliferative retinoblastoma exhibit altered gene copy numbers and expression of oncogenes and tumour suppressor genes. These additional modifications following RB1 inactivation during retinoblastoma development progressively lead to resistance of tumour cells to cell death, including resistance to chemotherapeutic agents.

Aims of the study
We aimed to target mitochondria, a key element in the different programmed cell death pathways, i. e. apoptosis, autophagy and necroptosis, with small therapeutic drugs to induce tumoural cell death. We aimed to highlight new factors involved in retinoblastoma tumour progression in order to develop new therapeutic approaches to counteract any tumoural modification and any cell death resistance.

Methods
Cellular and animal models are used to characterize involved signalling pathways and to study the effect of new therapeutics molecules.

Results
The study focusing on the mitochondria revealed that two molecules, BIRO1 and ABT-737, trigger cell death in human retinoblastoma cell lines. In *in vivo* studies, BIRO1 and ABT-737 drugs were injected intravitreally in the retinoblastoma mice model. Whereas ABT-737 was ineffective in inducing tumoural cell death alone, its efficiency was enhanced in combination therapy with an E2F inhibitor. BIRO1 was able to reduce tumour growth with inappropriate side effects on healthy retina, promoting massive death of the intact retinal cells. In the second part of the project, several factors were highlighted in retinoblastoma development, and we are now studying the validation of their functional role in tumour progression using cellular and zebrafish models.

Potential benefits for patients
The discovery of new therapeutics molecules should allow better management and treatment of the advanced stages of the disease. In addition, as the RB1 gene is found mutated in various cancer types, these new drugs should have a more general impact in oncology.

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Schwaller Jürg | **Dissecting the cellular origin and molecular targets in MLL acute leukaemia**
(KFS 2778-02-2011)

Chromosomal translocations leading to the expression of mixed lineage leukaemia (MLL) fusion genes are hallmarks of poor prognosis in patients with acute leukaemia. However, there are remarkable differences from patient to patient that are not fully understood. Previous studies have shown that MLL fusions act as aberrant transcriptional regulators and activate a myriad of downstream target genes that are essential for their leukaemogenic activity.

Biochemical studies revealed that MLL fusion proteins form dynamically assembled multi-protein complexes binding to their target gene promoters. Here we used a novel and fully reversible transgenic mouse model for the acute myeloid leukaemia (AML)-associated MLL-AF9 fusion to address the role of the cellular origin for the clinical outcome. We were able to show that activation of the fusion in haematopoietic stem cells resulted in a significantly more aggressive disease than activation in more committed progenitor cells. Comparative gene expression profiling of mouse leukaemia and AML patients allowed us to identify several origin-related downstream targets that were associated with a poor clinical outcome.

These genes are currently being validated for their role for induction and maintenance of MLL-fusion gene induced leukaemia. We also explored the possibility of directly interfering with the MLL-fusion complex by dissecting the critical domains of its interaction with the lens epithelial-derived growth factor (LEDGF) adapter protein. Here we identified two critical protein-protein interfaces that can potentially be targeted by small molecules. Moreover, we performed a large RNA interference-based screen to search for potentially pharmacologically blockable protein kinases that are essential for the leukaemogenic activity of MLL-fusion proteins.

We have identified over 50 candidates mediating growth, survival, self-renewal and/or aberrant differentiation of MLL-AF9 immortalized cells. Current efforts aim to further validate their role for induction and maintenance of the disease in multiple *in vitro* and *in vivo* models. Taken together, our work has provided experimental proof of concept that the cellular origin is a critical factor of disease outcome in AML induced by MLL fusion proteins. Our work also identified several target genes that might not only serve as prognostic biomarkers but could also open the way for origin-related therapeutic interventions.

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Thome-Miazza Margot | **Analysis of the role of the protease MALT1 in human lymphomas**
(KFS 2561-02-2010)

The activation and subsequent proliferation of lymphocytes is part of the normal immune response to infection. This process is altered in leukaemias and lymphomas because of cellular alterations that allow an unlimited proliferation of lymphocytes. Our objective was to explore the role of the protease MALT1 in this process, since MALT1 plays an important role in lymphocyte proliferation. By comparing normal and activated lymphocytes, we showed previously that MALT1 protease activity is detectable only in activated lymphocytes. In addition, we showed that MALT1 is hyperactive in a particular subtype of lymphoma, the ABC-DLBCL, and that MALT1 inhibition leads to impaired growth of such cancer cells *in vitro*.

The goal of this project was to investigate whether MALT1 protease activity is also relevant for other lymphoma cell types, such as cutaneous T-cell lymphomas and lymphomas induced by the oncogenic human herpesvirus-8 (HHV-8). In cell lines derived from human cutaneous lymphomas, no MALT1 activity was detectable. However, treatment with a MALT1 inhibitor was toxic to a latently HHV-8-infected B-cell lymphoma cell line. In addition, we identified two viral proteins of HHV-8 as potential MALT1 substrates. These findings suggest a potential role for MALT1 in HHV-8-induced lymphomas that we will further explore. We hope that these investigations of the relevance of MALT1 in different lymphomas will lead to new strategies in their diagnosis and treatment.

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Widmann Christian | **The 317–326 sequence of RasGAP as potential anti-metastatic agent**
(KFS 2543-02-2010)

Dissemination of cancer cells from a primary tumour is one of the events most dreaded by oncologists. Indeed, metastasis formation is the main cause of death due to cancer. We discovered previously that a peptide derived from a fragment of the RasGAP protein is capable *in vitro* of increasing the adhesiveness of cells to their substratum and of blocking their migratory activity. Based on these properties, it can be envisioned that this peptide has anti-metastatic activities.

In this project, we confirmed the capacity of the RasGAP-derived peptide to inhibit the invasion capacity of tumour cells. We also demonstrated that the activity borne by the peptide was able to inhibit metastatic progression in a murine tumour model. Identification of the peptide's tar-

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get would facilitate the development of anti-metastatic compounds. Therefore, we looked for proteins that could be required for the anti-metastatic activity of the Ras-GAP-derived peptide. We found that the DLC1 tumour suppressor was not only necessary for the peptide to increase cell adherence and block cell migration but that the peptide was able to bind DLC1. DLC1 is thus a direct target of the peptide.

We can thus now search for small molecules that are able to bind DLC1, as the peptide does, and determine whether these molecules have anti-metastatic activities. If they do not induce too strong side effects, these compounds could be used in patients to diminish the risk of metastasis formation after the primary tumour is treated by surgery, chemotherapy or radiotherapy, for example.

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Wymann Matthias P. | **Identification and modulation of targets to reprogramme glioblastoma cancer stem cells** (KFS 2680-08-2010)

Glioblastoma multiforme (GBM) is a very aggressive brain tumour. A signalling pathway connecting a lipid kinase (phosphoinositide 3-kinase (PI3K)) to a nutrient sensor complex (target of rapamycin, mTOR) constitutes a central piece of GBM aetiology. Up to now, little is known regarding relevant signalling downstream of PI3K. Exploring structural determinants of putative phosphoinositide-interacting proteins, we assembled pathway modules to be targeted in GBM.

We developed enrichment protocols for GBM-derived cancer stem cells (GBM CSCs). Monitoring phenotypic outputs of pharmacologically and genetically modulated PI3K-dependent pathways revealed two interdependent protein kinases that are key to GBM proliferation. Inhibition of these protein kinases drives GBM cells towards differentiation and cell death. Mechanistic studies and

first small molecules with a "proof-of-concept" status indicate that the knowledge gained should be further pursued with the aim to develop novel treatment strategies for this devastating disease.

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Zavolan Mihaela | **Identification of cancer-related targets of individual members of the miR-17-92 cluster of miRNAs** (KFS 2477-08-2009)

MicroRNAs (miRNAs) are small (22 nucleotides long) RNA molecules that form complexes with the Argonaute proteins, guiding these proteins to protein-coding transcripts to induce their degradation and to repress the production of proteins. MiRNAs are thereby involved in many important cellular processes such as cell division, viability, differentiation and self-induced death. Aberrant expression of individual miRNAs leads to various diseases, including cancers, in which miRNAs play either a facilitating role (oncogenic miRNAs or oncomirs) or an inhibitory role (tumour suppressor miRNAs). Among the oncogenic miRNAs, one of the most studied is the cluster of miR-17-92 miRNAs, which are encoded in a single gene, from which six individual miRNAs are processed. The protein-coding targets and thereby functions of the individual miRNAs in the cluster are not well understood.

In this study we employed high-throughput experiments with computational modelling and biochemical follow-up studies to determine the targets of individual miR-17-92 cluster members. An important part of our study consisted in the development of the experimental methods that allow us to isolate binding sites of miRNAs with very high resolution, from minimally manipulated cells. These methods consist in the crosslinking of proteins to RNAs with ultraviolet light in living cells, followed by the isolation of the Argonaute protein together with the associated RNAs, and sequencing of the Argonaute-bound RNA fragments that represent the miRNA binding sites. Analysis of these data revealed that although individual miRNAs do not concertedly act on their targets, they target functionally related genes and pathways.

Among the top targets that we identified with our methods is the important tumour suppressor PTEN, which is targeted by the miR-19a miRNA, factors that are involved in cell division and death, such as the cyclin D2 and the transcription factor E2F1, which are controlled by miR-17, Aurora kinase-A and the MDM2 ubiquitin ligase that are regulated by miR-19a, and components of the miRNA pathway itself, particularly the miRNA-processing enzyme DICER1 and the Argonaute-associated factor TNRC6b, which are controlled by miR-18. Although the responses of these complex networks to perturbations are difficult to predict, we expect that the targets that we found to be bound by miR-17-92 cluster miRNAs *in vivo* will lead to a better understanding of the oncogenic role of this miRNA cluster.

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Further completed research projects in 2013

Dufour Jean-François | KFS 2541-02-2010 | CHF 202,200.–
Universitätsklinik für Viszerale Chirurgie und Medizin, Universität Bern, Bern
Hepatocarcinogenic roles of mTOR, raptor and rapamycins in absence of Pten

Krek Wilhelm | KFS 2690-08-2010 | CHF 226,000.–
Institut für Zellbiologie, ETH Zürich, Zürich
Roles of the URI oncoprotein in B-RAF signalling and melanoma cancer cell proliferation

Petrova Tatiana | KLS 2570-02-2010 | CHF 198,300.–
Centre pluridisciplinaire d'oncologie (CePO), Centre hospitalier universitaire vaudois (CHUV) et Université de Lausanne, Epalinges
Lymphatic endothelial calcineurin/NFAT signalling in tumour lymphangiogenesis and metastasis

List of approved research projects in 2013

Total funds allocated: CHF 5,624,000.–

Affolter Markus | KLS 3177-02-2013 | CHF 111,800.–
Departement Biozentrum, Universität Basel, Basel
Cellular analysis of tumour neoangiogenesis in the zebrafish embryo

Auwerx Johan | KFS 3082-02-2013 | CHF 203,300.–
Laboratory of Integrative and Systems Physiology, EPF de Lausanne, Lausanne
The role of the sirtuin ageing proteins on the development of colorectal cancer

Bachmann Martin | KFS 3111-02-2013 | CHF 239,800.–
Dermatologische Klinik, Universitätsspital Zürich, Zürich
Bispecific anti-tumour antibodies: combining tumour-specificity with cytokine agonism

Caflisch Amedeo | KFS 3098-02-2013 | CHF 249,900.–
Biochemisches Institut, Universität Zürich, Zürich
Development of ATAD2 bromodomain inhibitors to fight breast and lung cancer

Carbone Giuseppina | KFS 3243-08-2013 | CHF 241,800.–
Laboratorio di oncologia sperimentale, Istituto oncologico della Svizzera italiana (IOSI), Bellinzona
Deregulated ETS transcriptional network and clinical implications for prostate cancer progression

Cejka Petr | KFS 3089-02-2013 | CHF 249,600.–
Institut für Molekulare Krebsforschung, Universität Zürich, Zürich
Maintenance of genome stability by hDNA2 in complex with BLM or WRN proteins

Clavien Pierre-Alain | KFS 3262-08-2013 | CHF 144,400.–
Klinik für Viszeral- und Transplantationschirurgie, Universitätsspital Zürich, Zürich
Inositol tris-pyrophosphate (ITPP) and its anti-hypoxic potential in colorectal metastases of the liver

Dormond Olivier | KFS 3128-02-2013 | CHF 227,600.–
Service de chirurgie viscérale, Centre hospitalier universitaire vaudois (CHUV), Lausanne
Mechanisms of acquired resistance of cancer cells to PI3K inhibition

Fajas Lluis | KFS 3236-08-2013 | CHF 210,600.–
Département de physiologie, Université de Lausanne, Lausanne
Cancer-induced metabolic changes in the host organism: beyond the Warburg effect

Foti Michelangelo | KFS 3246-08-2013 | CHF 209,300.–
Département de physiologie cellulaire et métabolisme, Université de Genève, Genève
Role of miR-22 in hepatocellular carcinoma

Gilliet Michel | KLS 3161-02-2013 | CHF 221,300.–
Service de dermatologie et vénéréologie, Centre hospitalier universitaire vaudois (CHUV), Lausanne
Targeting intracellular nucleic acid receptors for melanoma immunotherapy

Hall Jonathan | KFS 3293-08-2013 | CHF 229,500.–
Institut für Pharmazeutische Wissenschaften, ETH Zürich, Zürich
Targeting the Lin28/pre-let-7 interaction in cancer

Hantschel Oliver | KLS 3132-02-2013 | CHF 225,400.–
Institut suisse de recherche expérimentale sur le cancer (ISREC), EPF de Lausanne, Lausanne
Identification and targeting of allosteric regulatory sites in oncogenic cytoplasmic tyrosine kinases

Huelsken Joerg | KFS 3135-02-2013 | CHF 229,800.–
Institut suisse de recherche expérimentale sur le cancer (ISREC), EPF de Lausanne, Lausanne
Immunotherapy against cancer stem cells

Lefort Karine | KFS 3301-08-2013 | CHF 197,500.–
Département de biochimie, Université de Lausanne, Epalinges
Notch signalling in lung squamous cell carcinoma

Levesque Mitchell | KLS 3151-02-2013 | CHF 201,900.–
Dermatologische Klinik, Universitätsspital Zürich, Zürich
Functional genomics of melanoma heterogeneity and invasion

Michielin Olivier | KFS 3180-02-2013 | CHF 236,700.–
Service d'oncologie médicale, Centre hospitalier universitaire vaudois (CHUV), Lausanne
Adoptive cell transfer for stage IV melanoma using rationally designed TCR

Müller Antonia | KFS 3183-02-2013 | CHF 201,900.–
Klinik für Hämatologie, Universitätsspital Zürich, Zürich
Improving graft-versus-tumour effects by donor vaccination with WT1-peptide and transplantation of tailored haematopoietic grafts

Münz Christian | KFS 3234-08-2013 | CHF 214,000.–
Institut für Experimentelle Immunologie, Universität Zürich, Zürich
Collaboration of Epstein Barr virus and Kaposi sarcoma-associated herpes virus during lymphomagenesis

Schäfer Beat W. | KFS 3238-08-2013 | CHF 229,500.–
Abteilung Onkologie, Kinderspital Zürich, Universitäts-Kinderkliniken, Zürich
Novel in vivo models of rhabdomyosarcoma tumourigenesis

Swartz Melody | KFS 3312-08-2013 | CHF 247,400.–
Institut interfacultaire de bioingénierie, EPF de Lausanne, Lausanne
Targeting tumour-associated lymphatics for cancer immunotherapy

Thome-Miazza Margot | KFS 3265-08-2013 | CHF 216,900.–
Département de biochimie, Université de Lausanne, Epalinges
Identification of a ubiquitin ligase driving lymphomagenesis

Tritschler Isabel | KFS 3305-08-2013 | CHF 246,600.–
Klinik für Neurologie, Universitätsspital Zürich, Zürich
TGF-β family members and proprotein convertases: potential therapeutic targets in glioblastoma?

van den Broek Maries | KFS 3233-08-2013 | CHF 214,000.–
Institut für Experimentelle Immunologie, Universität Zürich, Zürich
The role of immune defense and platelets in the development of spontaneous metastases

Weller Michael | KLS 3110-02-2013 | CHF 223,700.–
Klinik für Neurologie, Universitätsspital Zürich, Zürich
CD317 immunotoxin therapy for glioblastoma

Zaugg Kathrin | KLS 2901-02-2012 | CHF 199,800.–
Universitätsklinik für Radio-Onkologie, Inselspital, Universitätsspital Bern
Dose-rate effect of novel radiation technologies: relevance for the clinical use

Approved bursaries in 2013

Total funds allocated: CHF 685,000.–

Bonalli Mario | MD PhD 3237-06-2013 | CHF 145,000.–
Isolation and characterization of novel transcription factors involved in neural crest stem cell maintenance and melanoma formation
Destination: Anatomisches Institut, Universität Zürich, Zürich

Bührer Elias | MD PhD 3238-06-2013 | CHF 180,000.–
The role of CD27 signalling in acute myeloid leukaemia
Destination: Universitätsklinik für Medizinische Onkologie, Inselspital, Universitätsspital Bern, Bern

Jauch Annaïse | MD PhD 3239-06-2013 | CHF 180,000.–
The role of TSLP mediated inflammation in melanoma development and progression
Destination: Institut suisse de recherche expérimentale sur le cancer (ISREC), EPF de Lausanne, Lausanne

Waeber Sabine | MD PhD 3240-06-2013 | CHF 180,000.–
The role of inflammation in cancer progression: contribution of myeloid-derived suppressor cells (MDSC) and the pro inflammatory cytokines IL-1β and IL-18
Destination: Institut universitaire de pathologie de Lausanne (IUP), Centre hospitalier universitaire vaudois (CHUV), Lausanne

Basic biomedical research

Presentation of approved research projects in 2013

Affolter Markus | **Cellular analysis of tumour neoangiogenesis in the zebrafish embryo**
(KLS 3177-02-2013)
Duration: 01.04.2013 – 31.03.2014

The connection between tumour growth and tumour neoangiogenesis has been a long-standing interest in basic angiogenesis research and for applied cancer treatment. One therapeutic approach that has emerged recently is founded on the observation that tumour vessels are often disorganized and do not support efficient blood flow, thus causing a chronic hypoxic condition within tumours. This hypoxia promotes metastatic behaviour of tumour cells, which is further aided by the fact that tumour blood vessels are often leaky and thus facilitate tumour cell extravasation.

These observations have led to the proposition that tumour metastasis may be effectively suppressed and the efficacy of chemotherapy increased by normalizing the tumour vasculature. Despite the enormous efforts put into angiogenesis research, it has remained difficult to characterize the cellular events underlying angiogenesis. This is due to the fact that live imaging approaches have thus far not been possible to develop in mice. More recently, the zebrafish has been used to study angiogenesis and tumour development using live imaging.

We will use our expertise on live imaging of angiogenesis processes in the zebrafish in order to better characterize the process of tumour neoangiogenesis. We will characterize in detail the cellular activities (cell migration, cell polarization, lumen formation, cell rearrangements) during neoangiogenesis and compare them to developmental angiogenesis processes. Using chemical and genetic manipulations, we will investigate whether any abnormalities in tumour vessels might be reverted or enhanced. These studies should produce better insights into tumour neoangiogenesis at the cellular and molecular level.

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Auwerx Johan | **The role of the sirtuin ageing proteins on the development of colorectal cancer**
(KFS 3082-02-2013)
Duration: 01.01.2014 – 31.12.2016

Colorectal cancer is the consequence of an interaction between genetic predisposition and environmental factors, which include in particular age, diet and chronic inflammation. Sirtuins are a group of enzymes that are extremely well conserved in the animal kingdom. In mammals, the sirtuin protein family is composed of seven related proteins, SIRT1 to SIRT7. Although similar in structure and activity, these different sirtuin proteins are present in distinct tissues and in different cell compartment (nucleus or cytoplasm).

We propose here to identify the impact of SIRT1, 6 and 7 (named SirtX below), which are the three sirtuins that are present in the cell nucleus, on colitis-associated colorectal cancer (CAC) using a multifaceted strategy using genetically engineered mouse models in which the Sirtuin genes are deleted specifically in the intestine ($SirtX^{int-/-}$).

Our strategy is based on achieving the following three specific aims: (1) generation and global characterization of intestinal-specific SirtX$^{int-/-}$ deficient mice, (2) determination of the role of intestinal specific SirtX gene deletion in the onset of CAC, and (3) characterization of SirtX-driven pathways involved in CAC development. Since the activity of the sirtuins proteins can be easily modified by small molecules (such as a number of drugs), the eventual confirmation of the relevance of nuclear sirtuins in colitis-associated colorectal cancer will lay the foundations for future new treatments for this disease.

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Bachmann Martin | **Bispecific anti-tumour antibodies: combining tumour-specificity with cytokine agonism**
(KFS 3111-02-2013)
Duration: 01.07.2013 – 30.06.2016

The immune system has the capacity to fight cancer, and strong local immune responses may result in shrinkage or even elimination of tumours. Such inflammation is mediated by cytokines. By targeting pro-inflammatory cytokines to a tumour, it may be possible to harness the immune system for treatment of cancer. Here we will develop novel molecules in the mouse that allow the targeting of pro-inflammatory cytokines into tumours and testing of their anti-tumour activity in murine models of cancer. If successful, similar biologics will be developed for use in humans.

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Caflisch Amedeo | **Development of ATAD2 bromodomain inhibitors to fight breast and lung cancer**
(KFS 3098-02-2013)
Duration: 01.04.2013 – 31.03.2016

Epigenetic proteins, influencing which genes are expressed, represent a promising and new area of research for targeted cancer therapeutics. The ATAD2 protein is one such target that is highly expressed in several types of solid tumours, and its overexpression is correlated with rapid mortality in breast and lung cancer. We will identify and validate small molecules that selectively inhibit the binding of the bromodomain region of ATAD2 to histone proteins around which DNA is wound, through a multidisciplinary approach.

Our strategy involves: (1) computational simulations to characterize regions of ATAD2 forming selective interactions with identified small molecules (Amedeo Caflisch), and (2) synthesis and medicinal chemistry-optimization of promising compounds to improve their potency, selectivity and pharmaceutical properties (Cristina Nevado, Department of Chemistry, University of Zurich). The resulting collection of inhibitors will be tested on several tumour cell lines to shed light on the role of ATAD2 in cancer. Promising compounds will be further developed and tested on mice models in view of their human application.

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Carbone Giuseppina | **Deregulated ETS transcriptional network and clinical implications for prostate cancer progression** (KFS 3243-08-2013)
Duration: 01.01.2014 – 31.12.2015

Prostate cancer is the most common cancer in men and a leading cause of cancer death in developed countries. Prostate cancer has very heterogeneous clinical behaviour, ranging from indolent to aggressive forms. Once the disease progresses, there are limited treatment options. Thus, an important issue is to identify the factors that determine tumour behaviour and find more specific treatment strategies for the different tumour subtypes. Our data indicate that deregulated expression of ETS transcription factors plays important role in disease progression and tumour heterogeneity.

The overall goal of this study is to apply novel strategies for molecular classification of prostate tumours and to further understand the biology of prostate cancer. To reach these goals we will combine novel bioinformatic approaches using multiple datasets from primary and metastatic prostate tumours with functional experiments in cell lines *in vitro* and *in vivo*. We plan to evaluate critical pathways in tumours with altered ETS expression, with particular emphasis on alterations of epigenetic effectors to understand the mechanisms of their deregulation and their influence on disease progression. This knowledge will represent an important step towards understanding the molecular and clinical heterogeneity of prostate tumours and will open new avenues for assessment of the prognosis and application of context-dependent therapeutic strategies.

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Cejka Petr | **Maintenance of genome stability by hDNA2 in complex with BLM or WRN proteins**
(KFS 3089-02-2013)
Duration: 01.04.2014 – 31.03.2018

Deoxyribonucleic acid (DNA) stores genetic information that is essential for the proper function of all living organisms. The replication and maintenance of DNA integrity and the repair of damage in DNA is thus an essential process. Defects in these mechanisms may lead to cancer.

We are investigating the function of the key DNA repair protein DNA2. DNA2 was found to be overexpressed in various human cancers, and high expression correlated with poor prognosis. However, the exact function of DNA2 remains unknown. We are going to identify the protein partners of DNA2, which will point towards its cellular role. Further, we will determine its biochemical activity on a number of model DNA substrates. Finally, we will investigate the relationship of DNA2 to BLM and WRN proteins. All these factors function in multiple complex processes that affect cancerogenesis. Detailed understanding of these molecular mechanisms will lay a groundwork that will be important for the design of future treatment strategies.

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Clavien Pierre-Alain | **Inositol tris-pyrophosphate (ITPP) and its anti-hypoxic potential in colorectal metastases of the liver** (KFS 3262-08-2013)
Duration: 01.02.2014 – 31.01.2016

Inositol tris-pyrophosphate (ITPP) is an extraordinary drug that increases tissue oxygen levels without any toxicity. Most solid tumours feature low oxygen levels (hypoxia), which are thought to promote tumour aggressiveness and spread (i.e. metastasis formation, the primary cause of death due to cancer).

We propose to study the efficacy and working mode of ITPP in colorectal (CRC) liver metastases. To do so we have established two liver metastasis mouse models and a non-invasive method for tumour follow-up. First trials have confirmed the antihypoxic action of ITPP that translates into improved survival of tumour-laden mice. We now are analysing tissue to assess the malignant potential of ITPP-treated tumours. A specific focus will be on the long-term effects of ITPP.

To estimate how ITPP might perform in patients, we will compare the standard treatment for CRC liver metastasis (FOLFIRI chemotherapy plus bevacizumab, a tumour vessel inhibitor) with FOLFIRI plus ITPP. Tumour vessels are functionally compromised, and their inhibition is suspected to increase the metastatic risk. In contrast, ITPP is expected to stabilize tumour vessels and hence to reduce this risk. Together with its highly favourable toxicity profile, ITPP has an unmatched anticancer potential that needs to be explored.

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Dormond Olivier | **Mechanisms of acquired resistance of cancer cells to PI3K inhibition** (KFS 3128-02-2013)
Duration: 01.01.2014 – 31.12.2015

Targeting oncogenes has been viewed as a promising approach in cancer therapy. In this context, a protein called PI3K is a promising target. Indeed, activating mutations of this enzyme are frequent in human cancers, which results in tumour growth. For this reason, several PI3K inhibitors have been developed and have been tested in clinical studies. Overall, the anti-cancer efficacy of PI3K inhibitors is modest, suggesting that cancer cells develop resistance mechanisms to these inhibitors. It is therefore important to identify these mechanisms in order to design new therapies aiming to ameliorate the anticancer efficacy of PI3K inhibitors.

In preliminary studies, we observed that PI3K inhibitors block AKT, a downstream effector of PI3K, only transiently. This suggests that cancer cells are able to reactivate AKT signalling in the presence of PI3K inhibitors to counteract the anticancer efficacy of these inhibitors. In this study, we therefore aim to identify the molecular mechanisms that drive AKT activity in the presence of PI3K inhibitors. Using different approaches, we wish to identify at the molecular level the mechanisms that reactivate AKT following PI3K inhibition. Once these mechanisms are identified, we plan to design therapeutic strategies combining PI3K inhibitors with inhibitors that block AKT reactivation. These strategies will then be tested in various models both *in vitro* and *in vivo*.

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Fajas Lluis | **Cancer-induced metabolic changes in the host organism: beyond the Warburg effect**
(KFS 3236-08-2013)
Duration: 01.01.2014 – 31.12.2015

It has long been known that the metabolism of cancer cells is very different from normal cells. This project focuses mainly on lipid metabolism. Lipids (fat) are among the most important molecules in the cell. This is especially important as a cell becomes cancerous. Indeed, cancer cells produce their own lipids. This is called “de novo synthesis”. In this research project we aim to find out how cancer cells trigger this process of production of lipids. The second important objective of the project is to understand how our bodies adapt to cancer growth. Cancers take over the control of our whole body metabolism to create the best conditions for growth. Our studies will identify new targets involved in the metabolism of cancer cells.

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Foti Michelangelo | **Role of miR-22 in hepatocellular carcinoma** (KFS 3246-08-2013)
Duration: 01. 04 .2014 – 30. 03. 2016

Hepatocellular carcinoma (HCC) is a frequent cancer and the third cause of cancer-related death in the world. HCC develops in the setting of various liver diseases, including viral infections, alcohol consumption, obesity and diabetes. Given the worldwide rise in obesity and diabetes, incidence of HCC is expected to dramatically increase in the future. HCC is a cancer with a very poor prognosis, and surgical resection or liver transplantation are the only treatments with (poor) curative potential. However, critical issues are associated with these therapies, and it is necessary and urgent to explore other ways to treat HCC.

Recently, numerous studies have demonstrated the role of microRNAs in cancer. In particular, an aberrant expression of a specific microRNA, the miR-22, is associated with several common and deadly human cancers (e. g. breast, lung, colorectal, pancreas and prostate) including HCC. These recent observations suggest that miR-22 likely plays an important role in cancer development. However, direct *in vivo* evidence establishing the importance and role of miR-22 in carcinogenesis is lacking. The goal of this project is to investigate *in vitro* and *in vivo* in mice, the role of miR-22 in liver carcinogenesis, with or without obesity as an additional risk factor. The potential therapeutic benefits of pharmacological miR-22 agonists on HCC will also be investigated.

Our experimental approach will integrate different mice models of HCC, in which miR-22 expression is genetically altered, or modulated by pharmacological treatments with miR-22 agonists. This will allow us not only to understand the role of miR-22 in liver cancer but also to envisage in the mid-term new therapeutic perspectives for HCC. In addition, these studies will likely provide important insights, new knowledge and concepts to understand and fight cancer in general.

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Gilliet Michel | **Targeting intracellular nucleic acid receptors for melanoma immunotherapy** (KLS 3161-02-2013)
Duration: 01. 08. 2013 – 31. 07. 2015

Treatment opportunities for metastatic melanoma remain poor, since chemotherapy and irradiation are of limited efficacy. Melanoma is a potentially immunogenic tumour, and immunotherapy seems to be a promising therapeutic strategy. However, the discovery of potent adjuvants is urgently needed. Studies of antiviral immunity have taught us that strong innate immune activation is pivotal for the induction of adaptive immune response mediated by T-lymphocytes and B-lymphocytes.

In this study, we generalize principles learned from successful antiviral vaccination to generate anti-tumour immunity with viral-like stimuli. Our hypothesis is that the targeting of intracellular nucleic acid receptors (important players in antiviral immunity) leads to the establishment of an anti-tumour immune response in a mouse model of melanoma. Our first aim is to improve efficacy of nucleic acid sequences with known anti-tumoural activity. We also want to investigate the capacity of signalling pathways described recently in antiviral immunity but not yet exploited in cancer immunotherapy. Lastly, we aim to uncover new molecules targeting intracellular nucleic acid sensors with efficient anti-tumoural activity. Thus, this research study will uncover new strategies to improve immunotherapy for metastatic melanoma or other patients with advanced-stage cancer.

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Hall Jonathan | **Targeting the Lin28/pre-let-7 interaction in cancer** (KFS 3293-08-2013)
Duration: 01. 01. 2014 – 31. 12. 2015

This project is a direct follow-on from the project *Targeting pre-let-7 biogenesis in cancer* (KFS 2648-08-2010). As described previously, many human cancers exhibit a dysregulation of microRNA expression in which they are non-functional or overexpressed. A prominent example is the let-7 family in which let-7 prevents normal cells from becoming tumourigenic. In several cancers levels of let-7 are very low. This is due to the RNA-binding protein Lin28, which binds to the precursor of let-7 preventing its correct processing. New studies have shown also that the Lin28/let-7 plays an important role in maintenance of cancer stem cells.

We synthesized short antisense oligonucleotides that bind to the let-7 precursor and protect it from degradation by Lin28. This leads to increased levels of let-7 in cells and inhibition of cancer cell growth. One goal of this study is to improve the properties of the antisense oligonucleotides through chemical modification. This should lead to a stronger effect on the precursor and will be examined in mouse cancer models. The results of the study will provide new insights into the mechanisms of anti-microRNA antisense oligonucleotides in living models of cancer.

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Fotogramm / Haselnuss, 2013

Hantschel Oliver | **Identification and targeting of allosteric regulatory sites in oncogenic cytoplasmic tyrosine kinases** (KLS 3132-02-2013)
Duration: 01.11.2013 – 31.10.2015

An important protein class with cancer-causing properties are protein kinases, which act as molecular switches and are normally in the off-position in normal cells. In contrast, kinases are always in the on-position in cancer cells. Since 2001, 22 new drugs have been discovered that are able to block the on-position of particular kinases and confine the growth of tumours. Unfortunately, patients with cancer often only benefit from these new drugs for a short time, as changes in the molecular structure of the kinase prevents effective action of the drug.

In this research project, we will attempt to understand alternative mechanisms by which kinases can be turned on, and to target them. To understand the underlying molecular mechanisms, we are preparing purified proteins to analyse their biochemical properties. In addition, cancer cells will be used to compare the normal kinase with variants that are impaired in these regulatory mechanisms for their ability to influence cell growth. Finally, we plan to identify molecules that bind the regulatory control site in one particular kinase that causes leukaemia. Altogether, this project can lead to the identification of additional ways in which tumour cells can be attacked, with the hope that these new insights can be translated into useful therapies for patients with cancer.

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Huelsken Joerg | **Immunotherapy against cancer stem cells** (KFS 3135-02-2013)
Duration: 01.01.2014 – 31.12.2015

One adverse characteristic of cancer is that tumours escape the control of the immune system. The concept of adoptive immunotherapy is focused on re-arming the immune system against cancer cells by using the patient's own T-cells. These cells are redirected against a new target and amplified in a laboratory setting before they are given back to the patient. This involves equipping the T-cells with a new kind of molecule (called the CAR construct), which combines the high specificity of an antibody together with the strong effector signals of the T-cell itself. With this molecule the T-cell can now escape suppressive mechanisms in the tumour and can again attack the cancer cells. When using this approach it is necessary to be as precise as possible to avoid unwanted side effects.

Our research is focused on targeting a specific tumour cell population that is mainly responsible for the outgrowth and spread of the cancer: cancer stem cells (CSCs). We will target these important cancer cells by novel CAR designs that allow us to specifically recognize these cells, generate a durable immune attack, and thereby prevent cancer progression and metastasis.

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Lefort Karine | **Notch signalling in lung squamous cell carcinoma** (KFS 3301-08-2013)
Duration: 01.01.2014 – 31.12.2015

Lung cancer is the main cause of death by cancer. Squamous cell carcinomas (SCCs) of the lung account for 30 % of lung cancer. Compared to lung adenocarcinoma, the main histological subtype, lung SCC is less well understood and has far fewer treatment options. The epidemiology of lung SCC is different from that of adenocarcinoma. A distinguishing feature of these tumours is their elevated degree of heterogeneity and differentiation, which may explain their resilience to conventional and novel targeted therapy. Conventional chemotherapy remains the cornerstone of SCC treatment, and there is an urgent need for improvement of treatment of this disease, which has a median overall survival of less than 1 year in metastatic patients.

Our study will assess the therapeutic potential of induction of squamous cell differentiation as a way to counteract the consequences of pro-oncogenic events linked with lung SCC development. To this purpose, we will use human normal epithelial bronchial cells as well as lung SCC cell lines to test whether activation of the Notch signalling pathway is required and sufficient to induce squamous differentiation of these cells and causes reversion of lung SCC cells to a more differentiated and less malignant phenotype. Finally, we will assess whether the pro-differentiation function of Notch signalling in lung epithelial cells is mediating or controlled by a network of squamous differentiation-associated genes that are commonly mutated in SCCs.

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Levesque Mitchell | **Functional genomics of melanoma heterogeneity and invasion** (KLS 3151-02-2013)
Duration: 01.05.2013 – 30.04.2016

By combining studies on human melanoma biopsies from the Zurich University Hospital biobank with an *in vivo* zebrafish melanoma invasion assay, we intend to identify and characterize the function of a core set of developmental genes that also enable metastasizing cancer cells to colonize new tissues during melanoma progression. Since metastasis is a highly dynamic process that occurs in a three-dimensional physiological space, the ability to switch between our *in vitro* melanoma assays and *in vivo* embryonic invasion assays will allow us to more effectively investigate this process of cell invasion in both developmental and pathological contexts.

Our work will therefore take two directions. First, to identify genes that have a role in both developmental and pathogenic cell invasion, we will test in human cancer cells the homologs of genes associated with zebrafish neural crest invasion. Second, we will use zebrafish larvae as an *in vivo* xenograph invasion assay to test the necessity and sufficiency of these genes to facilitate melanoma invasion.

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Michielin Olivier | **Adoptive cell transfer for stage IV melanoma using rationally designed TCR** (KFS 3180-02-2013)
Duration: 01.05.2013 – 30.04.2015

Adoptive cell transfer immunotherapy against cancer relies on the ability of immune system killer T-cells to recognize and specifically destroy cancer cells. This recognition is carried out by a receptor called TCR, which binds specifically at the surface of cancer cells, starting a cascade of biochemical events that will eventually destroy these cells. Adoptive cell transfer immunotherapy consists in extracting from the patient killer cells that are specific for the disease, expanding them ex vivo, and re-injecting them in the patient to create an efficient immune response against the tumour.

The goal of this project is to optimize TCRs binding specifically to melanoma cancer cells using rational protein engineering, to increase their binding affinity for tumour cells and thus their killing capabilities. The TCR that has been selected for this study belongs to the repertoire

targeting the NY-ESO-1 antigen, which is among the most specific cancer-testis antigens. NY-ESO-1 is of utmost importance in melanoma immunity. Patients who express NY-ESO-1 show a better response to treatment by the monoclonal antibody ipilimumab.

We have developed a new method based on binding free energy calculations that enables us to rationally modify the sequence of a TCR targeting NY-ESO-1. We have obtained a 150-fold increase in TCR potency for the binding to melanoma cancer cells. Engineering *in vitro* the patient T-cells to express these modified TCRs, we have been able to dramatically increase the immune response against melanoma cells. Based on these *in vitro* results, we are currently starting an *in vivo* test on a mouse model that will pave the way to a human clinical trial planned for 2016.

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Müller Antonia | **Improving graft-versus-tumour effects by donor vaccination with WT1-peptide and transplantation of tailored haematopoietic grafts** (KFS 3183-02-2013)
Duration: 01. 05. 2013 – 30. 04. 2016

Blood or marrow transplantation (BMT) is the only curative therapy for many patients with blood cancers. The host's blood system, including tumour cells, is eradicated by radio-/chemotherapy, and donor grafts containing blood stem cells and immune cells are infused. Donor immune cells recognize the patient's tumour cells as foreign, which is called "graft-versus-tumour" reactivity, and are thus critical for durable tumour eradication. But they also attack healthy host tissues; this is a potentially detrimental clinical condition called "graft-versus-host-disease" that kills 15–20 % of all BMT-recipients. Novel therapeutic strategies with both enhanced efficacy and better tolerability are urgently warranted.

Here, we propose to improve BMT by combining the cellular therapy with vaccination against the tumour. To obtain enhanced anti-tumour immunity, donors will be vaccinated against the recipient's tumour. These tumour-specific immune cells will be isolated and transplanted, together with blood stem cells, into tumour-bearing recipients. Blood stem cells sustain healthy blood production while the selected tumour-specific immune cells can expand in the recipient, attacking tumour cells only, and unspecific tissue damage can be avoided – as no other immune cells are transferred. A combined approach that generates potent immune populations in the donor that after transplantation exclusively target recipient's tumour cells without damaging healthy tissues would be a major advancement in the battle against cancer.

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Münz Christian | **Collaboration of Epstein Barr virus and Kaposi sarcoma-associated herpes virus during lymphomagenesis** (KFS 3234-08-2013)
Duration: 01. 02. 2014 – 31. 01. 2017

One fifth of all tumours in humans are presumably caused by infections. In this regard a subgroup of herpes viruses features prominently. Epstein Barr virus (EBV) causes among others Burkitt's lymphoma, which is still the most common childhood tumour in Sub-Saharan Africa, and Kaposi sarcoma-associated herpes virus (KSHV) is associated with the most common tumour in patients with AIDS, Kaposi sarcoma, and certain lymphomas.

We recently discovered that double-infection with both viruses, which occurs in primary effusion lymphoma in patients, allows us to establish persistent KSHV infection in a mouse model of the human immune system. This first small animal model of chronic KSHV infection shows cooperation of both viruses not only during infection but also for tumourigenesis. This model now allows us to study the contribution of KSHV in tumour formation and KSHV-specific immune responses as well as their protective value. These investigations should enable us to develop new molecular therapy approaches against this human tumour virus, and to evaluate vaccination strategies.

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Schäfer Beat W. | **Novel *in vivo* models of rhabdomyosarcoma tumourigenesis** (KFS 3238-08-2013)
Duration: 01. 01. 2014 – 31. 12. 2015

Sarcomas are rare paediatric cancers that are very aggressive. Treatment in certain subgroups is only effective in less than 50 % of cases, thereby highlighting the need to develop novel treatment strategies. To learn more about the development of this tumour, it is necessary to generate models that faithfully mimic human disease. Here, we propose to develop two novel models for the paediatric tumour alveolar rhabdomyosarcoma (aRMS).

The first method is based on recently developed techniques that allow reprogramming normal human cells such as fibroblasts into pluripotent stem-like cells. We now propose to use these techniques to reprogramme human aRMS cells from patients and thereby turn the wheel of tumour development backwards. Reprogrammed cells are allowed to progress through tumourigenesis either *in vitro* as organoid cultures or *in vivo* after subcutaneous injection into mice. This makes possible close monitoring of tumourigenesis characterization of individual steps on the molecular level. The second model is based on recent insights obtained from genetic studies of the human disease. These analyses have highlighted a few crucial genetic alterations. We will introduce these alterations into the mouse genome and expect that these mice will then develop tumours that are similar to the human disease.

These novel mouse models will aid evaluation of novel drugs in future preclinical studies. This is especially important for rare tumours, since too many new drugs are available to test them all directly in patients.

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Swartz Melody | **Targeting tumour-associated lymphatics for cancer immunotherapy** (KFS 3312-08-2013)
Duration: 01.03.2014 – 28.02.2017

Lymph node metastasis of many cancers, including breast and cervical cancer, is the leading cause of cancer mortality. Lymph nodes that contain metastases are typically surgically removed, and tumour-associated lymphatic vessels have mainly been considered as routes for tumour dissemination.

The lymphatics play an important role in guiding immune cell homing and may play an active role in defining the immune status of the tumour microenvironment. Lymphatics are therefore an interesting and novel target, not just for the prevention of metastasis but also for therapies targeting the "re-regulation" of the local immune cell population towards an efficient anti-tumour response. We hypothesize that tumours can use lymphatic vessels and drainage to lymph nodes to reprogramme the immune system, promoting immunological tolerance.

This research study will explore this new hypothesis in mouse models of spontaneous breast and cervical cancers. Specifically, we will determine how tumour-associated lymphatics and their drainage to the lymph node affect host immunity to the tumour and explore strategies to reverse this immunological tolerance. We believe that this research will introduce a new paradigm to our understanding of how tumours modulate the host immune system, leading to new therapeutic strategies targeting lymphatic vessels and tumour-draining lymph nodes for helping to drive efficient anti-tumour immune responses.

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Thome-Miazza Margot | **Identification of a ubiquitin ligase driving lymphomagenesis** (KFS 3265-08-2013)
Duration: 01.05.2014 – 30.04.2017

The proliferation of lymphocytes is normally tightly controlled. Defects in this process can promote an unlimited proliferation of lymphocytes, which results in the development of leukaemias or lymphomas. Our objective is to explore the molecular mechanisms underlying the control of lymphocyte proliferation in a particularly aggressive form of diffuse large B-cell lymphoma (DLBCL). Our previous work revealed that the activity of the protease MALT1 plays an important role in this type of malignant lymphocyte proliferation, in which MALT1 is hyperactive because of its modification by an unknown ubiquitin ligase. This suggests that the unknown ubiquitin ligase responsible for MALT1 ubiquitination could be a good drug target for the treatment of such MALT1-dependent cancers.

The goal of this study therefore is to identify the ubiquitin ligase responsible for MALT1 activation by a combination of biochemical and genetic approaches, and to further characterize the relevance of this enzyme for the growth of lymphoma cells. We believe that this may pave the way for the development of small molecule inhibitors of the ubiquitin ligase responsible for MALT1 ubiquitination, which could be a rational strategy to treat aggressive DLBCL.

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Tritschler Isabel | **TGF-β family members and proprotein convertases: potential therapeutic targets in glioblastoma?** (KFS 3305-08-2013)
Laufzeit: 01.02.2014 – 31.01.2016

Glioblastoma is the most aggressive subtype of the gliomas, a group of intrinsic brain tumours. Glioma cells release immunosuppressive molecules such as transforming growth factor (TGF)-β. Moreover, TGF-β promotes invasiveness of glioma cells and regulates their stem cell properties. Although the family of TGF-β family ligands consists of 33 proteins, preclinical and clinical therapeutic approaches have focused on TGF-β, whereas the role of other members of the TGF-β family has remained underexplored.

We aim at identifying the role of the respective TGF-β family proteins as well as the proprotein convertases (PCs) that may be responsible for processing the TGF-β-related proproteins especially in glioma stem cells. The results of this work will be fundamental in determining the value of the specific inhibition of distinct ligands of the TGF-β superfamily as well as of the use of the appropriate PC inhibitors in patients with gliomas.

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van den Broek Maries | **The role of immune defense and platelets in the development of spontaneous metastases** (KFS 3233-08-2013)
Duration: 01. 04. 2014 – 31. 03. 2017

Tumour-specific immunity occurs in cancer patients and tumour-bearing animals, and significantly contributes to control of cancer. Metastasis – the major cause of death associated with solid tumours – may form even before the primary tumour becomes clinically apparent. Such early metastases remain in a dormant state for a considerable time, which means that the cancer cells hardly divide. Therefore, metastases are insensitive to therapies that target dividing cells such as radiotherapy or chemotherapy, whereas they can still be targeted by T-lymphocytes. Our first goal is to investigate how tumour-specific immunity can be employed to better control metastatic lesions.

Two recent studies in humans found that patients with a heart condition who were taking aspirin for a very long time because of this had a lower risk of dying of cancer. Because aspirin affects platelets and platelets promote the formation of metastases, our second goal is to investigate whether the anti-platelet effect of aspirin is responsible for the protection from lethal cancer. We think that our results will provide novel and essential knowledge on the interaction between metastatic tumours and the immune system. We expect that this knowledge will contribute to developing better immunotherapies that are efficacious in controlling metastatic lesions in men.

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Weller Michael | **CD317 immunotoxin therapy for glioblastoma** (KLS 3110-02-2013)
Duration: 01. 02. 2014 – 31. 01. 2016

Glioblastoma is the most common malignant primary brain tumour. Half of the patients die within 10 to 12 months after start of treatment, despite improved therapeutic options including surgery, radiotherapy and temozolomide chemotherapy. Therefore, innovative strategies to fight these brain tumours are urgently needed. In an attempt to follow the ideas of Paul Ehrlich's "magic bullet", we intend to investigate a new therapeutic molecule that consists of an antibody fragment coupled to a toxic protein. A designer protein-toxin consisting of a single chain Fv (scFv) fragment binding to the tumour cell and pseudomonas exotoxin A (ETA') as a toxic moiety will be analysed. This conjugate binds to CD317 (HM1.24), which is highly expressed on certain tumours including glioblastomas.

In initial cell culture experiments, the HM1.24-ETA' immunoconjugate showed promising results. HM1.24-ETA' is humanized and therefore should be well tolerated. After binding to CD317, this antibody-based toxin will be internalized, and the free toxic moiety of ETA' kills the tumour cell. In addition, interferon-α/β, a cytokine naturally produced in the body, can induce the expression of CD317 on the cell surface of glioblastoma cells.

We will analyse the effect of this immunoconjugate HM1.24-ETA' on brain tumour cells in cell culture. In a next step, the effect of HM1.24-ETA' will be evaluated alone or in combination with interferon-β in a brain tumour model in mice. These studies should provide the basis for an innovative specific immunotoxin therapy in combination with interferon-β for glioblastoma patients.

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Further approved research project 2013

Zaugg Kathrin | KLS 2901-02-2012 | CHF 199,800.–
Universitätsklinik für Radio-Onkologie, Inselspital, Universitätsspital Bern
Dose-rate effect of novel radiation technologies: relevance for the clinical use

Research and development in tumour surgery: The importance of team work

Surgery continues to be one of the most important pillars of cancer treatment. Of all treatment options available today, surgery with a nearly 100 % response rate is by far the most effective method of removing a tumour completely.[1] Tumour surgery had its renaissance in the 1970s and 1980s, when most of the principles and techniques were established that are still valid today. In recent years we have learned that the basis of successful cancer treatment is, for one, understanding the tumour biology, and for another, combined-modality treatment.

Advances and problems

Surgical treatment of bone or soft tissue tumours, the sarcomas, has a model character for tumour surgery. Sarcomas are much less common than carcinomas (such as breast, prostate or colorectal cancer) and represent only about 1 % of all human cancers. Sarcomas can form in connective or supportive tissue (bone, cartilage and fat) or in muscle tissue. They are rare, and in contrast to carcinomas, they grow in a centripetal fashion, and there are satellite cells in the reactive zone, which is why the entire sarcoma must be removed in the first operation. Sarcomas can be treated successfully only through the combination of surgery, radiation therapy and chemotherapy.

There were enormous advances in sarcoma surgery techniques in past decades.[2,3] Today, it is possible to avoid amputation of limbs for a majority of patients. Despite this fortunate development, we have to report that in the last 15 years, the advances in surgical techniques have become increasingly smaller, and we are still struggling with the same problems and complications, which include infections, prosthetic stem loosening, and loss of function. In parallel, the survival rates of patients with sarcomas have remained constant. Too many patients with sarcomas die because we cannot remove the primary tumour completely or because metastases have developed.[4]

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Fotogramm / Mehrfachbelichtung eines Lochs, 2011

Patient benefit as the goal

The main goal of tumour surgery is local removal of the primary tumour with as few negative functional consequences as possible for the patient. But the development of metastases and the spread of cancer cells in the body cannot be prevented primarily by the scalpel. Despite the treatment options available today, approximately 30 % to 40 % of patients with sarcomas die. To improve patient survival rates it is imperative that we also take the biology of the tumour into account. Through further innovations in tumour surgery alone we can at best maintain current success rates.

Combined-modality treatment as the recipe for success

Before the principles of modern tumour surgery were established, soft tissue sarcomas, for example, were either removed or radiated. This concept was then replaced more and more by a combination of the two treatment methods. Radiotherapy has the potential to eliminate satellite cells. This in turn allows the sarcoma surgeon to remove a tumour that lies close to a neurovascular bundle without damaging the motor function of the body part in question or without having to reconstruct the vessels. This functional benefit for the patient can be further improved with radiation treatment prior to surgery, as in this way the negative consequences of radiation on the soft tissue can be further reduced. Saving limbs and their function thus came about not through improved surgery but through development of a combination of treatments. The key to progress in research and medicine therefore lies in interdisciplinary team work.

Necessary paradigm change

We need to think less in terms of areas of expertise and instead put a greater focus on patient benefit. Of course it is important to study and further develop surgical techniques. Examples here are cryotherapy (local use of freezing techniques), microwave therapy, pasteurization, photodynamic therapy, and the latest radiosurgery techniques like Gamma Knife or NanoKnife. For this, we need large numbers of patients in the framework of international studies. However, studies of that kind are difficult to conduct, for with the exception of the Netherlands, tumour surgery patient data are not systematically registered in any European country.

The question is therefore not how sarcoma surgery is developing per se but instead in what direction the treatment of patients with bone and soft tissue sarcomas should develop to reduce side effects while maintaining the same effectiveness. We need to work in an interdisciplinary way, define a common basis and take that basis as our guide. Little is achieved if we have highly specialized sub-disciplines but the persons involved do not speak the same language or if there is insufficient exchange. Research that is not aimed at patient benefit has only limited potential to bring further advances.[5] To the most pressing questions at present, we have basic and simple answers with which we are very familiar. But the problem lies in inadequate implementation.

Interdisciplinary sarcoma boards

Surgeons are often of the opinion that a tumour must be surgically removed for evaluation primarily, so that thereafter – depending on the pathology results – the further therapies can be conducted. Today it is imperative that each sarcoma patient is discussed in an interdisciplinary sarcoma board before any treatment at all is undertaken.[6]

Unplanned operations without prior biopsy

Still today, in more than one-fourth of all patients with sarcoma there is unplanned removal of a tumour, where subsequently and surprisingly a sarcoma is diagnosed – either due to improvident decisions at critical moments, as these tumours are so rare, or because established surgical principles are violated.[7,8] In Switzerland there are still too many patients for whom these first operations lead to unnecessary amputations or who die as a result of this treatment error. Unfortunately, there is some resistance against facing up to this internationally known problem. Most probably, as the example of the Netherlands shows, the problem can be tackled only with higher level, political measures.

Drug therapies

In cancer medicine we expect that chemotherapy mainly affects the tumour cells. Here we monitor in particular the side effects, whereas we take the main effect as a matter of course. We know that the drugs in standard chemotherapy are biodistributed in the body through diffusion. It has been shown that they almost accumulate in the healthy organs everywhere and that uptake is the least in the tumour and in the targeted organ itself.[9] In view of this, for clinical use of an anticancer drug, why must not also the affinity to the tumour and thus the tumour uptake of the drug be demonstrated prior to demonstrating that it works locally against cancer cells?[6]

Clinical studies

Due to the fact that patient survival has plateaued over the years, intensive attempts are being made to employ new, "targeted" drugs also with patients with sarcoma. The mechanism of action of these therapies is based on simple mutations or expression differences of individual biomarker proteins of tumour cells. Although there are successful examples here (such as in the treatment of gastrointestinal stromal tumours), we have to accept that they will remain exceptions.[10] Even scant molecular knowledge suffices to understand that in the face of the immense heterogeneity of tumour cells, the problem is much more complex than would allow the targeting of a simple molecular change to work for the majority of tumours.[11] It is again and again astounding how a substance can be put into clinical trials with so little preclinical validation evidence from laboratory and animal trials.[12] Apparently, the pressure to obtain positive results is great. Today a drug is already considered successful if it lengthens the time period to tumour recurrence by a mere three months, without affecting the overall patient survival rate.

Promoting translational research

The common denominator of all of these aspects is biology. Our understanding of tumour biology has increase exponentially in the last 20 years. Unfortunately, this knowledge is not finding its way into clinical treatment, because clinicians and biologists live in separate worlds and there is too little exchange between them.[6] We know that the strategy for treating sarcoma that we have followed for years has not brought any appreciable advances. If we want to improve patient survival, we must change our thinking. We must bring clinical research and basic research closer together, in the sense of translational research. Biology must be given more priority in daily clinical practice. Before a clinical study is

even launched, we need much more evidence of the effectiveness of the substance to be studied.[13] At the same time, a tumour surgeon lacking an understanding of the biology of cancer cells should no longer be allowed to remove a tumour.

Foundations for progress

For collaboration among all disciplines involved in sarcoma treatment, we have to create structural and clinical prerequisites.[14–17] As already mentioned, part of this means that the treatment strategy for each patient with a sarcoma should be determined by an interdisciplinary sarcoma board[7] made up of all specialists, experts and tumour biologists.[18,20,21] As especially in sarcoma treatment a lot of knowledge is based on experience and not always on evidence, it is all the more important to define common and universally accepted treatment guidelines.[19,22–25] Data on the diagnosis and treatment of every sarcoma patient must be registered, and this can be handled best in the framework of a national cohort study. Ideally, the cohort data set should linked with a sarcoma tissue bank that contains tissue from primary tumours and possibly metastases as well as blood serum, which will make possible further patient-specific analyses in addition to the clinical data.

Last year we founded the *Swiss National Sarcoma Advisory Board*, which aims to implement these objectives. A common national platform will be established to address pressing questions at the national and international levels in a targeted and coordinated way, so that our understanding of tumour biology and the treatment of patients with sarcoma can be systematically improved. As mentioned at the start of this article, future developments in tumour surgery should not be viewed in isolation and in individual disciplines but rather must be defined in the context of inter.

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List of completed research projects in 2013

Ammann Roland A. | KFS 2933-02-2012 | CHF 63,300.–
Abteilung für Hämatologie/Onkologie, Universitätsklinik für Kinderheilkunde, Inselspital, Universitätsspital Bern, Bern
The impact of lowering fever limits on the rate of fever in chemotherapy induced neutropenia (FN): a prospective single-centre observational study in children and adolescents with cancer (Paediatric FN Definition 2012 Berne)

Bodis Stephan | KFS 2779-02-2011 | CHF 195,500.–
Institut für Radio-Onkologie, Kantonsspital Aarau, Aarau
Pilot study to assess the feasibility and toxicity of preoperative external beam radiotherapy for glioblastoma multiforme

Buess Martin | OCS 1825-02-2006 | CHF 167,000.–
Medizinische Onkologie, St. Claraspital, Basel
Understanding the pathophysiology of breast cancer gene expression profiles by in vitro analysis of the tumour-stroma interaction

Carbone Giuseppina | KFS 2573-02-2010 | CHF 305,100.–
Laboratorio di oncologia sperimentale, Istituto oncologico della Svizzera italiana (IOSI), Bellinzona
Deregulated ETS transcriptional network and clinical implications for prostate cancer progression

Carbone Giuseppina | KFS 2869-08-2011 | CHF 136,200.–
Laboratorio di oncologia sperimentale, Istituto oncologico della Svizzera italiana (IOSI), Bellinzona
Identification and clinical relevance of microRNA networks regulated by ETS transcription factors in prostate cancer

Foti Michelangelo | KFS 2502-08-2009 | CHF 307,400.–
Département de physiologie cellulaire et métabolisme, Centre médical universitaire (CMU), Université de Genève, Genève
Role of dietary free fatty acids, microRNA-21, and PTEN in liver cancer

Gruber Günther | KFS 2527-02-2010 | CHF 150,700.–
Institut für Radiotherapie, Klinik Hirslanden, Zürich
BIG 3-07: a randomized phase III study of radiation doses and fractionation schedules for ductal carcinoma in situ (DCIS) of the breast

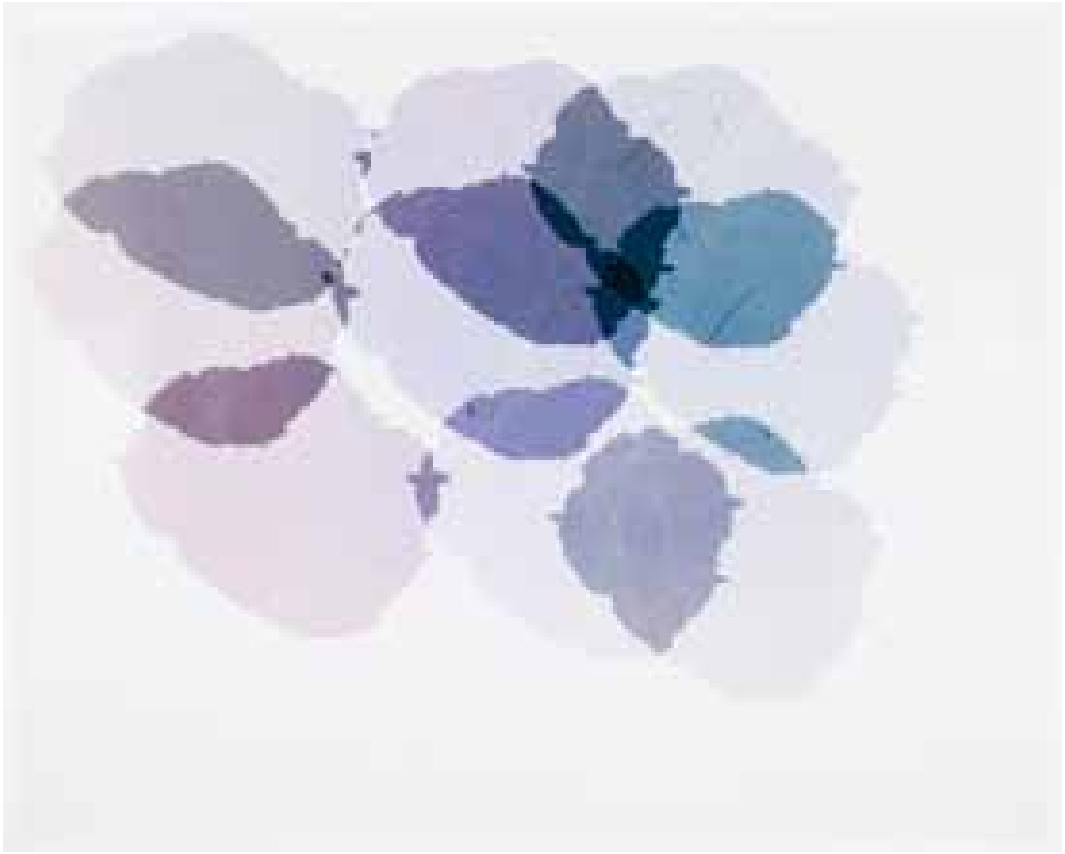
Jaggi Rolf | OCS 2132-08-2007 | CHF 309,800.–
Departement Klinische Forschung, Universität Bern, Bern
Molecular profiling from archival human breast cancer samples

Kalberer Christian | KFS 2872-08-2011 | CHF 188,800.–
Diagnostische Hämatologie, Universitätsspital Basel, Basel
In vitro expansion of human natural killer cells under good manufacturing practice conditions for immunotherapy of haematopoietic malignancies

Kristiansen Glen | KFS 2465-08-2009 | CHF 171,200.–
Institut für Pathologie, Universitätsklinikum Bonn, Bonn, Deutschland
Identification of a clinically applicable prognostic RNA signature of prostate cancer

Moeckli Raphaël | KFS 2637-08-2010 | CHF 107,200.–
Institut de radiophysique, Centre hospitalier universitaire vaudois (CHUV), Lausanne
Evaluation of second cancer risk models in radiotherapy for average and high dose levels

Müller Beatrice | KFS 2449-08-2009 | CHF 297,900.–
Abteilung für Hämatologie/Onkologie, Universitätsklinik für Kinderheilkunde, Inselspital, Universitätsspital Bern, Bern
Transcriptional dysregulation during myeloid transformation in acute myeloid leukaemia (AML)



Fotogramm / Mehrfachbelichtung eines Lochs, 2013

Niggli Felix | KLS 2578-02-2010 | CHF 298,300.–
Abteilung Onkologie, Kinderspital Zürich, Universitäts-Kinderkliniken, Zürich
Constitution of a national study centre for the European acute lymphoblastic leukaemia trial (AIEOP-BFM ALL 2009) on behalf of the Swiss Paediatric Oncology Group (BFM-CH)

Ozsahin Hulya | KLS 2656-08-2010 | CHF 155,300.–
Unité d'onco-hématologie, Département de l'enfant et de l'adolescent, Hôpitaux universitaires de Genève (HUG), Genève
SIOPEL International Childhood Liver Tumour Strategy Group – a comprehensive research programme and a randomized trial for standard risk hepatoblastoma

Pabst Thomas | KLS 2520-02-2010 | CHF 349,100.–
Universitätsklinik für Medizinische Onkologie, Inselspital, Universitätsspital Bern, Bern
Transcriptional dysregulation of the myeloid key transcription factor CEBPA in human acute myeloid leukaemia

Roth Arnaud | KFS 2697-08-2010 | CHF 202,700.–
Unité d'oncochirurgie, Hôpitaux universitaires de Genève (HUG), Genève
Molecular heterogeneity and prognostic markers in colon cancer by analysis of gene expression and gene mutation data

Presentation of completed research projects in 2013

Ammann Roland A. | **The impact of lowering fever limits on the rate of fever in chemotherapy induced neutropenia (FN): a prospective single-centre observational study in children and adolescents with cancer (Paediatric FN Definition 2012 Berne)**
(KFS 2933-02-2012)

The most frequent potentially lethal complication of chemotherapy in patients with cancer is fever in neutropenia (FN, fever and deficiency of white blood cells). Today, thanks to emergency hospitalization and empiric intravenous broad-band antibiotics, less than 1 % of children with FN die. However, bacterial infections are detected in only one-quarter of FN, which implies overtreatment in the remaining three-quarters. One possibility to reduce this overtreatment is to diagnose FN less frequently by setting a high fever limit. This limit is used inconsistently today in paediatric oncology, with a range from 37.5° C to 39° C. It is unknown if a higher fever limit is efficacious (reduces the number of FN diagnoses) and safe (does not increase complications due to delayed diagnosis and therapy).

Aim of the study
To quantify the rate of FN diagnoses when hypothetically lowering the fever limit below 39° C (efficacy).

Methods
In Bern, the highest known fever limit of 39° C is used clinically. In this prospective observational single-centre study, the efficacy of different fever limits can thus be studied by simulation without changing diagnosis and treatment of FN in reality.

Results
The study was completed as intended. In 39 children and adolescents with cancer, 43 FN episodes were diagnosed, 32 of them at temperatures ≥ 39° C, during 289 months chemotherapy exposure time. The fever limit 39° C versus lower limits relevantly reduced the number of FN diagnoses. For example, with a fever limit of 38° C, 31 additional FN would have been diagnosed. In 19 (61 %) of them, the hospitalization and antibiotics implied would have been useless, because in reality, spontaneous defervescence without specific measures was observed. As expected, a fever limit of 38° C would have led to an earlier FN diagnosis and correspondingly earlier start of antibiotics in the majority of FN episodes (median, 1.4 hours).

Conclusions
Only the efficacy, but not the safety, of high temperature limits was studied here. This is the reason why this study itself will not lead to changes in clinical policies. The design of an interventional multicentre study, aiming also at safety questions, builds upon these results, however.

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Bodis Stephan | **Pilot study to assess the feasibility and toxicity of preoperative external beam radiotherapy for glioblastoma multiforme**
(KFS 2779-02-2011)

The life expectancy of patients with glioblastoma multiforme (GBM) is short despite nearly six weeks of postoperative chemoradiation. This study explored the feasibility of short course, hypofractionated pre-operative radiotherapy (25 Gray over five days) followed by neurosurgery and adjuvant chemotherapy.

Our aim was to improve patients' quality of life (QoL) by shortening the course of radiotherapy by 5 weeks. We hypothesized comparable treatment efficacy without additional toxicity as compared to standard multimodality therapy. Further, any reduction in the vascularity might enhance maximal safe tumour resection. GBMs are challenging to treat, as the extent of microscopic spread is difficult to assess. Diffusion tensor imaging (DTI) is an MR-based technique that can show disruption of water diffusion as a surrogate for tumour spread, and application of DTI to radiotherapy planning was explored.

We successfully recruited three patients; however, there were no subsequent patients who met the eligibility criteria that were necessary for patient safety. The patients were able to receive preoperative radiotherapy without acute complications, and surgery proceeded as scheduled. Patients 2 and 3 developed postoperative infections that may or may not have been connected to the biopsy and irradiation, given the incidence of postoperative infection on the ward at the time. Patients 1 and 3 received chemotherapy according to protocol and subsequently received stereotactic re-irradiation of recurrent tumours without complication. All patients succumbed to their disease within the expected time frame for this diagnosis (overall survival of 16, 10 and 13 months).

As far as can be evaluated, the primary endpoint to deliver preoperative radiotherapy appeared safe and feasible. Collaboration with a neuropathologist is planned to evaluate paired diagnostic biopsy material and irradiated resected tumour. We successfully developed a technique to utilize diffusion tensor imaging in radiotherapy planning and presented this at major US, European and Swiss radiation oncology meetings (ASTRO, ESTRO and SASRO).

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Buess Martin | **Understanding the pathophysiology of breast cancer gene expression profiles by *in vitro* analysis of the tumour-stroma interaction**
(OCS 1825-02-2006)

The interaction between malignant tumour cells and adjacent stroma cells plays an important role in the onset and the progression of cancer. Specific molecular mechanisms are involved in tumour-stroma interaction. However, to date there is no satisfactory overview of the interactions at the molecular level. Gene expression profiling with DNA microarrays provides a detailed picture of the molecules involved in cancer. For most human tumours, gene expression profiles had been generated, and tumour subtypes with different clinical outcomes could be characterized. Now the challenge is to elicit from this large amount of detailed information the pathophysiology underlying the gene expression patterns.

In recent years we began to use global gene expression analysis to characterize the effects of stromal cells on the cancer cells, in particular the interactions between stromal fibroblasts, osteoblasts, endothelial cells and breast cancer cells. We established analytical tools, thereby demonstrating the variety of tumour-stromal cell interactions. As a hallmark of tumour-endothelial interaction, we identified a link between a C44+/CD24- stem cell-like gene expression signature and highly aggressive, unfavourable prognostic breast carcinomas. To further characterize the functional effects and their associated molecular properties, we used an *in vitro* co-culture model of human breast cancer cells and endothelial cells.

Our data suggest that endothelial cells induce morphological changes and cell migration in certain breast cancer cells. Gene expression analysis generated a list of genes that are important for cell migration. This effect is mediated by as yet unknown secreted factors. Further, we found an IL-6 gene expression pattern induced by heterotypic interaction of breast cancer cells with osteoblasts *in vitro*, which was associated with a higher rate of bone metastasis *in vivo*.

With this series of *in vitro* experiments and correlation with data from human tumour tissue banks, we will continue to identify targets for new therapeutic strategies, which aim at the function of tumour endothelial cells, regardless of angiogenesis. In addition, with the detailed gene expression analysis, we hope to establish new prognostic and predictive markers for the treatment of breast cancer.

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Carbone Giuseppina | **Deregulated ETS transcriptional network and clinical implications for prostate cancer progression** (KFS 2573-02-2010)

Prostate cancer is a leading cause of cancer death in Western countries. ETS transcription factors are important elements in the pathogenesis of prostate cancer, and chromosomal translocations involving ETS genes are very common. In this grant application, we proposed to study clinical and functional impact of ETS factors alone and in combination and to apply ETS-based molecular classification of prostate tumours for diagnosis and therapeutic applications.

To reach this goal, we integrated data from clinical samples with molecular and functional studies in several ETS cell models. Accordingly, we studied the ETS gene family in normal prostate and primary prostate cancers and found that in addition to the translocated ETS genes, other ETS factors are frequently affected in prostate tumours in the absence of gene rearrangements. In particular, members of the epithelial-specific ETS subfamily ESE3/EHF and ESE1/ELF3 were frequently altered in prostate tumours.

We showed that ESE3/EHF acts as a tumour suppressor, whereas ESE1/ELF3 has oncogenic properties in prostate epithelial cells. Further, our data uncovered important links of ETS factors with crucial pathways involved in progression and resistance to therapy, such as epigenetic, inflammation and stemness. Our data also indicated that there is an association between specific ETS alterations and prostate cancer progression. Overall, our studies resulted in a deeper understanding of the pathogenesis of prostate cancer and in clinically relevant findings.

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Carbone Giuseppina | **Identification and clinical relevance of microRNA networks regulated by ETS transcription factors in prostate cancer**
(KFS 2869-08-2011)

ETS transcription factors have proved to be important factors in the pathogenesis of prostate cancer. We recently reported deregulated expression of several ETS factors in prostate tumours and showed that they controlled key genes involved in the pathogenesis and progression of prostate cancer.

In these studies, we proposed to identify the network of microRNAs directly regulated by ETS transcription factors in prostate. Accordingly, integrating multiple data from prostate cancer patients and functional assays in cell lines, we discovered novel microRNAs regulated by ETS factors and demonstrated that they play a significant role in prostate cancer progression. The results of these studies led to the discovery of novel alterations of microRNAs in prostate tumours that may have important impact on diagnosis and management of prostate patients. Therefore, these studies led to clinically significant results. Knowledge of this kind is expected in the future to translate to significant benefit for patients with prostate cancer.

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Foti Michelangelo | **Role of dietary free fatty acids, microRNA-21, and PTEN in liver cancer**
(KFS 2502-08-2009)

Diabetes and obesity represent important risk factors for the development of liver cancer such as hepatocellular carcinoma (HCC). Indeed, accumulation of fatty acids in the liver (steatosis) occurs with obesity and diabetes and represents the first stage of metabolic liver diseases, which can progress towards HCC with time. One mechanism by which aberrant accumulation of fat in the liver contributes to carcinogenesis is by inducing the expression of small RNA molecules called microRNAs, which play an important role in cancer. In particular, microRNA-21 is upregulated in hepatocytes by fatty acids and thereby inhibits the expression of an important tumour suppressor called PTEN.

In this project, we investigated the role of dietary fats, microRNA-21 and PTEN in the development of pre-cancerous stages of the liver and HCC using various rodent models of these diseases. In particular, we generated a new transgenic mouse lacking the oncogenic microRNA-21 in hepatocytes.

Our results showed first that microRNA-21 is increased, and PTEN is decreased, in the liver of human obese subjects having steatosis and other disorders preceding the development of HCC. Importantly, mice lacking microRNA-21 in the liver were protected against metabolic disorders associated with diet-induced obesity and against tumour development in response to chemical carcinogens. Genomic and proteomic analyses then allowed us to uncover *in vitro* and *in vivo* a whole network of oncogenes and tumour suppressors that are affected by microRNA-21 and PTEN in the liver and that are potentially involved in hepatic carcinogenesis. Further characterization of the role of these microRNA-21/PTEN-dependent hepatic factors in HCC development is ongoing.

Our research should allow us to better understand the molecular basis of liver cancer, in particular in the setting of metabolic diseases. Also, the pertinence of future therapeutic interventions restoring normal microRNA-21 and PTEN activities in hepatocytes to prevent or to treat liver cancer is strongly supported by our results.

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Gruber Günther | **BIG 3-07: a randomized phase III study of radiation doses and fractionation schedules for ductal carcinoma *in situ* (DCIS) of the breast**
(KFS 2527-02-2010)

Patients with ductal carcinoma *in situ* (DCIS) of the breast are usually treated with breast conserving surgery and adjuvant/postoperative whole breast radiotherapy (WB-RT). In the BIG 3-07 trial, which is a collaborative trial all over the world, two main radiotherapy issues are under investigation: (1) the duration (shortening) of the WB-RT by using higher but fewer fractions, and (2) the increase of the total RT dose by giving what is called a "boost". Besides tumour-related outcomes (e. g. local failure rates), we also analysed quality of life (QoL) aspects.

Aim of the trial
To individualize the radiotherapy concept (RT duration; increase of the RT dose by a boost) for patients with DCIS after breast-conserving surgery in regard to local control and QoL.

Methods
Centres could choose to participate in a 2-arm (boost question) or 4-arm (boost and fractionation question) design. Patients were randomized to: (1) ARM A (25x WB-RT), or (2) ARM B (16x WB-RT), or (3) ARM C (ARM A+ 8x boost), or (4) ARM D (ARM B+ 8x boost). It is planned to analyse clinical and biological factors in regard to local failure (primary endpoint) as well as QoL aspects.

Results
Patient accrual will be reached successfully in June 2014, about two years ahead of schedule! Worldwide a total of 132 centres have participated in this trial. At the end of February 2014, 1 468 of 1,600 patients planned were included in the study (Arm A: 384; Arm B: 349; Arm C: 384; Arm D: 351). Up to 1 March 2014, eight Swiss centres contributed a total of 53 patients to the trial (Brustzentrum Zürich-Seefeld; Kantonsspital Graubünden; Universitätsspital Basel; Kantonsspital Münsterlingen; IOSI; Inselspital Bern; Kantonsspital St. Gallen; Klinik Hirslanden).

Potential gain for patients
Together with another ongoing French trial with patients with DCIS (2,000 patients planned), which will reach patient accrual within this year, the BIG 3-07 trail will help to individualize the radiotherapy concept in these patients. It is quite likely that the current study will define a new standard of care in the WB-RT of patients with DCIS.

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Jaggi Rolf | **Molecular profiling from archival human breast cancer samples** (OCS 2132-08-2007)

The oestrogen receptor can be detected in tumour cells from about 70 % of post-menopausal patients with distant, metastasis-free breast cancer. Binding of endogenous oestrogen activates the receptor, which in turn stimulates growth and proliferation of cancer cells. The effect can be inhibited or blocked in about 80 % of these patients by administering tamoxifen (Tam), an antagonist of oestrogen in breast cancer cells, or an inhibitor of endogenous synthesis of oestrogen such as letrozole (Let). Both drugs are similarly effective, with a slight advantage of Let over Tam. So far it has not been possible to identify patients who benefit specifically from one drug versus the other.

We used archival tumour tissue from patients enrolled in BIG 1-98, a large clinical trial with more than 8,000 postmenopausal patients with early, oestrogen receptor-positive breast cancer. About 2,000 patients were randomly selected and treated with Tam for 5 years; another 2,000

were treated with Let for five years. We obtained tumour tissue from approximately 300 patients. Half of them were treated with Tam and the other half with Let. Tumours were randomly selected but such that about half of the patients in each group (75 patients) had a relapse (either a metastasis or a local recurrence) and the other half (75 patients) remained relapse-free.

Total RNA was isolated from each tumour and used for our analysis. RNA has an important and central function in cells as carrier of genetic information that is stored in the nucleus of the cells from where it is translocated to the cytoplasm, where it is translated into protein. We quantitatively measured 190 RNAs that are of potential interest with regard to survival and/or response to Tam or Let treatment. A bioinformatics analysis was carried out to search for one or several RNAs in primary cancer tissue that correlated with critical clinical parameters like outcome or relapse in patients treated with Tam and/or Let.

We also studied whether several RNAs could be combined in a profile (often termed a signature or score) stably predicting the efficacy of one or both drugs. Indeed, we identified a group of nine genes that could be combined in a robust profile that we termed the "TamLet score". The score identified tumours that had a significantly better outcome when treated with Let rather than with Tam. Although TamLet was statistically significant in our study, the results need to be validated with material of independent but similar tumours. Once these additional tests are in agreement with our current results, TamLet has the potential to be used as additional, predictive parameter to inform the choice between two treatment options and to improve the outcome of some patients with primary, oestrogen receptor-positive breast cancer.

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Kalberer Christian | ***In vitro* expansion of human natural killer cells under good manufacturing practice conditions for immunotherapy of haematopoietic malignancies** (KFS 2872-08-2011)

The cytotoxic activity of human natural killer (NK) cells against acute myeloid leukaemia (AML) and plasma cell myeloma (PCM) is well established. The adoptive transfer of NK cells in the early post-transplantation period is a rational approach aimed at providing the patient with the benefit of competent anti-tumour effector cells. We previously showed that single NK cell donor lymphocyte infusions (NK-DLI) were safe and could revert graft rejections and promote long-lasting remission. The NK-DLI studies conducted by our clinic and by others indicated that high effector to target cell ratios will be necessary to obtain a significant anti-tumour effect *in vivo*. Our project is concerned with advancing immunotherapeutic NK cell trials to provide patients with NK cells with anti-tumour activity.

Towards this goal, we successfully implemented the NK cell expansion protocol in the newly available good manufacturing practice (GMP) facility of Basel University Hospital. The pre-clinical protocols were transcribed to standard operating procedures and validated under the clean room environment to comply with GMP regulations. By the end of 2013 we produced NK cells for one patient with AML and three patients with PCM. NK cells of healthy haploidentical family donors were purified after leukapheresis by T-cell depletion and NK cell selection. Starting from 2x1010 total nucleated cells, 6x108 NK cells were obtained with 96.5 % purity and a minimal T-cell contamination corresponding to a 5.5 log T-cell depletion efficacy. Purified NK cells were cultured in GMP medium containing growth factors interleukin-2 and interleukin-15 and irradiated feeder cells. Within 19 days NK cell numbers increased 55-fold. The NK cell products were cryopreserved as multiple units in escalating doses of up to 1.0x108 cells/kg body weight. The four patients received 20 NK-DLIs in total (3–8 doses), which were well tolerated without any acute adverse event. Infused NK cells were monitored by quantitative real-time PCR of donor DNA. We detected donor NK cells up to 20 hours after infusions, indicating prolonged survival in recipient's circulation.

These results demonstrate the feasibility of large-scale GMP expansion and of tolerability of multiple mega-dose infusions of human NK cells as immunotherapy after stem cell transplantation. The long-term follow-up will show whether this new treatment will contribute to an increased cure rate of patients with AML and PCM.

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Kristiansen Glen | **Identification of a clinically applicable prognostic RNA signature of prostate cancer** (KFS 2465-08-2009)

In the estimation of biological aggressiveness of prostate cancer, clinicopathological parameters do not always allow sufficient determination of the individual need for active therapy in a given patient. Formerly, almost all patients with a newly diagnosed prostate cancer received active treatment such as surgery or radiation therapy, but it has now been acknowledged that up to 30 % of patients are probably overtreated, since they would not have succumbed to their cancer even if they were never treated for it.

Study aims

We aimed to identify molecular prognostic markers that can be clinically applied by conducting a retrospective molecular analysis of clinically characterized prostate cancer cohorts.

Methods

Following an evidence-based compilation of suitable candidate genes, we extracted RNA from archival material using a protocol that was developed by the co-applicant, Prof. Rolf Jaggi, for paraffin-embedded tumour material. The expression levels of our target genes were measured by NanoString hybridization from three different cohorts (Zurich, Berlin, Erlangen).

Results
The bioinformatic evaluation revealed promising results for each of the analysed cohorts; however, we also found unexpected cohort-specific differences. Only four genes were similarly prognostic in all cohorts.

Potential benefit for patients
Our work demonstrates the necessity to verify also molecular prognostic markers in multiple cohorts, since a single demonstration of a prognostic value does not provide a sufficient basis for a test to be used for prospective assessment. The prognostic marker candidates that we found are going to be verified in further studies.

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Niggli Felix | **Constitution of a national study centre for the European acute lymphoblastic leukaemia trial (AIEOP-BFM ALL 2009) on behalf of the Swiss Paediatric Oncology Group (BFM-CH)**
(KLS 2578-02-2010)

Acute lymphoblastic leukaemia (ALL) is the most frequent cancer disease in children. Prognosis has been significantly improved over the last decades due to clinical treatment studies. Today, a combination of various cytostatic drugs allows a cure rate in over 80 % of all patients; however, treatment burden is considerable. Various clinical and biological factors, such as early treatment response, cytogenetic abnormalities in leukaemic cells, and minimal residual disease after a treatment period of several weeks have a significant influence on prognosis. According to these risk factors, treatment intensity will be adapted.

Aim of the study
The aim was to establish an international treatment concept for ALL with collaborating partners from Switzerland, Germany, Austria, Italy, Czech Republic, Israel and Australia. To realize this trial, a national study centre had to be built up for standardized diagnostics, data management and research facilities. This allows a risk-adapted treatment approach in children with ALL to further increase cure rate and to reduce treatment toxicity in subgroups. To reach this goal, standard treatment will be compared with new, potentially more effective treatment elements.

Results
We established a national study centre in Zurich, Switzerland, for this multicentre randomized clinical trial in ALL. This allows centralized reference diagnostics, laboratory analysis for measurement of minimal residual disease during the course of leukaemia treatment, as well as a common data registration and counselling for all newly diagnosed leukaemias in Switzerland.

During the first three years after study opening in Switzerland, 127 patients (65 % boys and 35 % girls) could be enrolled in the study; 55 % were between ages 1 to 5 years. This means that the vast majority of children in Switzerland with newly diagnosed ALL are managewithin a common treatment strategy. 24 % of the patients had to be treated in high risk group due to unfavourable cytogenetic features or a delayed treatment response to initial chemotherapy. Whether there is a further improvement of long-term survival within this study can only be analysed after a longer follow-up period and a higher number of patients enrolled in the study.

Summary
With the formation of a national study centre, children with ALL in Switzerland will benefit not only from a common treatment concept but also from a centralized platform for optimal diagnostics, advisory service, research facilities and data management.

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Pabst Thomas | **Transcriptional dysregulation of the myeloid key transcription factor CEBPA in human acute myeloid leukaemia** (KLS 2520-02-2010)

Improvement of therapeutic concepts in the treatment of patients with acute myeloid leukemia (AML) is an unmet medical need. In spite of intensive chemotherapy, up to 60 % of all patients with AML die of their disease. The wide application of autologous or allogeneic transplantation has not changed much in that perspective.

The concept of differentiation therapy is a promising novel approach. This is underlined by the success of the differentiation therapy with all-trans-retinoic acid (ATRA), exclusively effective in patients with acute promyelocytic leukaemia (APL). The myeloid transcription factor CEBPA is crucial for the differentiation of neutrophils. It specifically regulates the maturation at the myeloblastic stage: if CEBPA is blocked, myeloid maturation is arrested, and myeloblastic cells accumulate in the bone marrow and the blood, which exactly mirrors the situation observed in patients with AML.

In this project, we were investigating how the CEBPA protein is regulated in leukaemic cells. In addition, we investigated how CEBPA is regulated by a small class of novel regulatory molecules called microRNAs. In fact, we were able to demonstrate the regulation of CEBPA by two specific microRNAs. Ultimately, these results should aid in development of strategies aiming at restoring CEBPA function in leukaemic cells in a therapeutic context.

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Further completed research projects in 2013

Moeckli Raphaël | KFS 2637-08-2010 | CHF 107,200.–
Institut de radiophysique, Centre hospitalier universitaire vaudois (CHUV), Lausanne
Evaluation of second cancer risk models in radiotherapy for average and high dose levels

Müller Beatrice | KFS 2449-08-2009 | CHF 297,900.–
Abteilung für Hämatologie/Onkologie, Universitätsklinik für Kinderheilkunde, Inselspital, Universitätsspital Bern, Bern
Transcriptional dysregulation during myeloid transformation in acute myeloid leukaemia (AML)

Ozsahin Hulya | KLS 2656-08-2010 | CHF 155,300.–
Unité d'onco-hématologie, Département de l'enfant et de l'adolescent, Hôpitaux universitaires de Genève (HUG), Genève
SIOPEL International Childhood Liver Tumour Strategy Group – a comprehensive research programme and a randomized trial for standard risk hepatoblastoma

Roth Arnaud | KFS 2697-08-2010 | CHF 202,700.–
Unité d'oncochirurgie, Hôpitaux universitaires de Genève (HUG), Genève
Molecular heterogeneity and prognostic markers in colon cancer by analysis of gene expression and gene mutation data

List of approved research projects in 2013

Total funds allocated: CHF 5,096,600.–

Aebersold Rudolf | KFS 3309-08-2013 | CHF 245,700.–
Institut für Molekulare Systembiologie, ETH Zürich, Zürich
Molecular subclassification of non-small cell lung cancer by quantitative kinome interactome analysis

Bairoch Amos | KFS 3297-08-2013 | CHF 231,200.–
Sciences des protéines humaines, Université de Genève, Genève
Improving clinical interpretation of genetic variations underlying common cancers

Dietrich Pierre-Yves | KFS 3270-08-2013 | CHF 248,000.–
Centre d'oncologie, Hôpitaux universitaires de Genève (HUG), Genève
Development of chimeric antigen receptor T-cells for immunotherapy of glioma

Fix Michael | KFS 3279-08-2013 | CHF 221,600.–
Universitätsklinik für Radio-Onkologie, Inselspital, Universitätsspital Bern, Bern
Dosimetric evaluation and secondary cancer risk of modulated electron radiotherapy

Gerber Nicolas | KFS 3001-08-2012 | CHF 97,900.–
Abteilung Onkologie, Kinderspital Zürich, Universitäts-Kinderkliniken, Zürich
SIOP CNS GCT II: prospective trial for the diagnosis and treatment of children, adolescents, and young adults with intracranial germ cell tumours

Irminger-Finger Irmgard | KFS 3287-08-2013 | CHF 136,400.–
Département de gynécologie et d'obstétrique, Hôpitaux universitaires de Genève (HUG), Genève
BARD1, a molecular target for prostate cancer screening and therapy

Kalberer Christian | KLS 3190-02-2013 | CHF 224,300.–
Diagnostische Hämatologie, Universitätsspital Basel, Basel
Immunotherapy with mega doses of activated natural killer cells in haematopoietic malignancies and follow-up analysis of in vivo cell migration and survival

Krenger Werner | KFS 3237-08-2013 | CHF 179,900.–
Departement Biomedizin, Universität Basel, Basel
Role of sphingosine-1-phosphate (S1P) receptor agonism in engraftment, T-cell regeneration and anti-tumour immunity in preclinical and clinical haematopoietic stem cell transplantation

Kruithof Egbert | KFS 3163-02-2013 | CHF 111,700.–
Service d'angiologie et d'hémostase, Hôpitaux universitaires de Genève (HUG), Genève
Regulation of procoagulant activities of acute promyelocytic leukaemia cells

Langer Rupert | KFS 3083-02-2013 | CHF 236,000.–
Institut für Pathologie, Universität Bern, Bern
The impact of autophagy on biology and chemoresistance of oesophageal adenocarcinomas

Lugli Alessandro | KFS 3294-08-2013 | CHF 233,700.–
Institut für Pathologie, Universität Bern, Bern
MicroRNAs in the tumour microenvironment of colorectal cancer: novel targets for therapeutic intervention?

Matter Matthias | KFS 3302-08-2013 | CHF 214,000.–
Institut für Pathologie, Universitätsspital Basel, Basel
Identification of mechanisms that promote liver cancer

Mazzucchelli Luca | KFS 3266-08-2013 | CHF 214,000.–
Istituto cantonale di patologia (ICP), Locarno
MYC activation in diffuse large B-cell lymphomas

Nadal David | KLS 3189-02-2013 | CHF 235,200.–
Abteilung Infektiologie und Spitalhygiene, Kinderspital Zürich, Universitäts-Kinderkliniken, Zürich
Translational research with the goal to identify, characterize, and target B-ALL-specific and Burkitt's lymphoma-specific T-helper cells

Petrausch Ulf | KFS 3115-02-2013 | CHF 190,600.–
Klinik für Onkologie, Universitätsspital Zürich, Zürich
Phase I study for the adoptive transfer of re-directed FAP-specific T-cells in the pleural effusion of patients with malignant pleural mesothelioma

Rechsteiner Markus | KLS 3123-02-2013 | CHF 30,000.–
Institut für Klinische Pathologie, Universitätsspital Zürich, Zürich
Non-invasive identification of VHL mutations in plasma by deep-sequencing with subsequent assessment of mutant pVHL functionality in FFPE by FRET-FLIM in ccRCC patients

Reyes Mauricio | KLS 3167-02-2013 | CHF 228,300.–
Institut für Chirurgische Technologien und Biomechanik, Universität Bern, Bern
Medical image analysis for brain tumour studies

Rottenburger Christof | KFS 3170-02-2013 | CHF 217,500.–
Klinik für Radiologie und Nuklearmedizin, Universitätsspital Basel, Basel
^{177}Lu-PP-F11N for receptor-targeted therapy and imaging (theranostics) of metastatic medullary thyroid cancer – a pilot and a phase I study

Simon Hans-Uwe | KFS 3099-02-2013 | CHF 264,300.–
Institut für Pharmakologie, Universität Bern, Bern
Characterization of ATG5 as a tumour suppressor in cutaneous melanoma

Tausch Christoph | KFS 3300-08-2013 | CHF 249,900.–
Brust-Zentrum Zürich, Zürich
Randomized controlled trial to evaluate the impact of a surgical sealing patch on lymphatic drainage after axillary lymph node dissection for breast cancer

Theocharides Alexandre | KFS 3298-08-2013 | CHF 193,600.–
Klinik für Hämatologie, Universitätsspital Zürich, Zürich
The CD47-SIRPα interaction and the role of ikaros in myeloproliferative neoplasms

Fotogramm / Mehrfachbelichtung eines Lochs, 2011

Tornillo Luigi | KFS 3169-02-2013 | CHF 220,000.–
Institut für Pathologie, Universitätsspital Basel, Basel
Understanding the molecular mechanisms of differential responses to anti-angiogenic treatment in colorectal cancer

von der Weid Nicolas | KLS 3175-02-2013 | CHF 215,600.–
Onkologie/Hämatologie, Universitäts-Kinderspital beider Basel, Basel
Effects of a 1-year partially supervised exercise programme in childhood cancer survivors: a randomized controlled trial

von Gunten Stephan | KFS 3248-08-2013 | CHF 222,800.–
Institut für Pharmakologie, Universität Bern, Bern
Siglec-7/-9 ligand receptor interactions in NK cell-mediated tumour immunosurveillance

Zajac Paul | KFS 3149-02-2013 | CHF 234,400.–
Departement Biomedizin, Universitätsspital Basel, Basel
Investigator-initiated phase I immunotherapy trial for patients bearing non-small cell lung cancers expressing cancer/testis tumour antigens and treated with a non-replicating vaccinia virus encoding for 7 antigenic epitopes, CD80 and CD154 co-stimulatory molecules

Approved bursaries in 2013

Total funds allocated: CHF 576,600.–

Dawson Heather | BIL KFS 3252-08-2013 | CHF 42,000.–
Interaction between EMT-like cancer cells ("tumour buds") and blood/lymphatic vessel invasion in the tumour microenvironment of colorectal cancer
Destination: Faculty of Medicine, University of Toronto, Toronto, Canada

Fisher Oliver | BIL KLS 3133-02-2013 | CHF 127,000.–
Prognostic biomarkers and long non-coding RNA in oesophageal adenocarcinoma
Destination: St.Vincent's Centre for Applied Medical Research, Darlinghurst, Australia

Gonseth Nusslé Semira | BIL KLS 3124-02-2013 | CHF 96,900.–
Association between parental folate intake and specific epigenetic patterns in children with acute lymphoblastic leukaemia
Destination: Department of Epidemiology & Biostatistics, University of California, San Francisco, USA

Rozenholc Alexandre | BIL KLS 3148-02-2013 | CHF 147,800.–
Blue dye only vs. blue dye + technetium for sentinel node procedure in endometrial cancer
Destination: Centre hospitalier de l'Université de Montréal, Hôpital Notre-Dame, Montréal, Canada

Pauli Chantal | BIL KFS 3259-08-2013 | CHF 90,400.–
Genetics and epigenetics of high-grade myxofibrosarcoma: a next generation approach towards a better understanding of sarcomas with complex karyotypes
Destination: Department of Pathology and Laboratory Medicine, Weill Cornell Medical College, New York, USA

Schaffar Robin | BIL KFS 3274-08-2013 | CHF 72,500.–
Long-term net survival among women with breast cancer in Geneva
Destination: Department of Non-Communicable Disease Epidemiology, London School of Hygiene and Tropical Medicine, London, United Kingdom

Presentation of approved research projects in 2013

Aebersold Rudolf | **Molecular subclassification of non-small cell lung cancer by quantitative kinome interactome analysis** (KFS 3309-08-2013)
Duration: 01.01.2014–31.12.2015

This research project is centred around the quantification of the lung cancer proteome, which includes all proteins that can be measured by mass spectrometer. A particularly important subset of the proteome is the protein kinases and their interacting proteins. Protein kinases and their interactors form functional enzyme complexes that phosphorylate other proteins and as a result change their functionality. Kinase complexes play a key role in the initiation and progression of lung cancer.

The primary objective of this study is the identification and quantification of previously unknown disease-relevant kinases and their associated proteins in patients with early stages of lung cancer to facilitate a new classification of the disease. To study the lung cancer proteome, 43 tissue samples from individual patients were collected.

Further, fractions of lung tumours and adjacent healthy tissues will be lysed under high pressure and proteins will be extracted from the tissue. The extracted proteins are then enzymatically digested to peptides that are identified and quantified by mass spectrometry. The profiles kinase complex components of cancerous and normal tissues will be compared to dissect the disease-related changes in individual patients. Moreover, such kinase profiles could also predict the risk of recurrence after curative surgery and the survival potential of advanced tumour stage patients, thus significantly improving the treatment of patients with lung cancer.

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Bairoch Amos | **Improving clinical interpretation of genetic variations underlying common cancers**
(KFS 3297-08-2013)
Duration: 01.02.2014–31.01.2016

Modern technologies have made DNA sequencing sufficiently affordable to make it feasible to use the genome sequence as a diagnostic tool, at a cost that will soon be equivalent to that of any standard medical analysis. The rate-limiting step, both in terms of time and expertise, is the analysis of these results. This is especially true for patients with genetic diseases or cancers where it is difficult to uncover the mutations that are causative of the disease from all the benign variations. This problem is exacerbated for cancers, as cancerous tissues harbour numerous mutations, among which the mutations that are important for correct diagnostic and eventual treatment of the cancer are "hiding".

The aim of this project is to build a compendium of the mutations known or expected to be the cause of three clinically important types of cancers: leukaemia, Lynch syndrome and hereditary breast and ovarian carcinoma (HBOC). The work will be carried out using bioinformatics techniques, bioinformatics being the scientific field that helps derive knowledge from computer analysis of biological data. The project will significantly contribute to supporting clinicians in establishing and standardizing rules for more precise diagnosis of cancers.

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Dietrich Pierre-Yves | **Development of chimeric antigen receptor T-cells for immunotherapy of glioma**
(KFS 3270-08-2013)
Duration: 01.01.2014–31.12.2016

Brain cancer (mostly glioma) is a major public health problem, being the first cause of death by cancer in children and the third in young adults. Current treatments are poorly effective and patient outcome is dismal. Novel treatments are warranted. Here, we want to exploit the natural ability of the immune system to detect and kill cancer cells to design an innovative treatment strategy. We recently identified 10 targets that are exclusively or preferentially expressed by glioma cells and not by normal cells. The next step is now to guide the killer cells of the immune system towards these targets for a selective attack on tumour cells without damaging normal cells of the brain.

In this project, we will combine the natural properties of two components of the immune system, T-lymphocytes (that can kill tumour cells) and antibodies (that recognize cell surface targets). T-lymphocytes will be engineered to express an antibody acting here as a homing device to specifically guide killer T-lymphocytes to the glioma cell surface. These engineered T-lymphocytes are called chimeric antigen receptor cells (CARs). This project will allow engineering and selecting of the most effective CARs, which will then be used in future clinical trials, establishing a new treatment modality for patients with brain cancer.

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Fix Michael | **Dosimetric evaluation and secondary cancer risk of modulated electron radiotherapy**
(KFS 3279-08-2013)
Duration: 01.03.2014 – 28.02.2016

Recent technological developments in photon radiotherapy have led to complex treatment techniques (intensity modulated radiotherapy or volumetric modulated arc therapy) that result in better tumour targeting while sparing neighbouring healthy tissues. In contrast, electron radiotherapy remains at a very basic level, despite the interesting dosimetric properties associated with electrons: Indeed, due to their limited penetration depth in tissue (in contrast to photons), electron beams are well suited to treat shallow tumours and better spare healthy tissues at larger depths. Intensity and energy modulation of electron beams (known as MERT) could further improve the dosimetric quality of plans. MERT is more challenging than photon IMRT, as more sophisticated dose calculations algorithms are required and dedicated electron beam collimation systems are usually used.

Using Monte Carlo calculations, our group developed a treatment planning tool to create MERT plans for linear accelerators using the same collimation system as for the photon beams. This tool will be used to determine which sites will benefit most from MERT treatment compared to photon radiotherapy. In particular, we will assess the risk of late effects such as radiation-induced secondary cancers and cardiovascular disease. Finally, the impact of hardware- and patient-related uncertainties on the robustness of MERT plans will be assessed. These results will provide a further step towards clinical implementation of MERT.

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Gerber Nicolas | **SIOP CNS GCT II: prospective trial for the diagnosis and treatment of children, adolescents, and young adults with intracranial germ cell tumours** (KFS 3001-08-2012)
Duration: 01.09.2013 – 30.08.2016

Intracranial germ cell tumours are among the most common brain tumours in childhood and adolescence. Through the introduction and optimization of surgical treatment, chemotherapy and radiotherapy, the cure rate in these patients has increased from 20 % to more than 80 %. However, not all patients can be cured, and at the same time, the treatment can cause significant acute and late toxicity. With the current treatment protocols, some patients appear to be undertreated, and for other patients treatment is unnecessarily strong.

The international study SIOP CNS GCT II is trying to better tailor the treatment to the individual needs of the patient according to the tumour subtype, the extent of spread and the response to therapy. For example, in patients with a relatively favourable prognosis (i. e. germinoma), the radiation field is extended to the whole ventricular system (since in the previous study, most relapses were observed in the ventricles); however, in patients with a good tumour response to the preceding chemotherapy, the radiation dose is reduced. For another subgroup of patients with a worse prognosis, chemotherapy is intensified using high-dose chemotherapy.

Although germ cell tumours belong to the most common brain tumours in children, adolescents and young adults, the absolute number of approximately four new cases a year in Switzerland is low. Therefore, the treatment of these diseases can only be further optimized in international multicentre studies of this kind. All Swiss paediatric oncology centres are taking part in this study protocol.

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Irminger-Finger Irmgard | **BARD1, a molecular target for prostate cancer screening and therapy**
(KFS 3287-08-2013)
Duration: 01.01.2014 – 31.12.2015

Prostate cancer is the most frequently diagnosed cancer in most Western countries. A general risk factor is androgen, but genetic predisposition, linked to mutations in breast cancer genes BRCA1 and BRCA2, becomes evident. Early detection is necessary for a favourable diagnosis, but the screening for the prostate-specific antigen (PSA) has not led to a reduced death rate. Thus, novel biomarkers and treatment targets are urgently needed.

We found that BARD1, known as tumour suppressor interacting with BRCA1 and important for breast cancer, is present in modified forms that act as oncogenes in breast and many other cancers. We propose to define which of the aberrant forms of BARD1 are specifically expressed in prostate cancer and how this is correlated with patient diagnosis and outcome. We will determine the cellular and environmentally regulated (epigenetic) factors that drive their expression and how we could interfere. These oncogenic forms of BARD1 are also immunogenic and trigger the production of circulating antibodies.

We will develop a diagnostic or screening test, based on detection of such BARD1 antibodies. We have already shown in proof of principle studies that such a test is possible for breast (Patent WO2012038932) and lung cancer (Patent WO2012023112). We are aiming at a blood test for prostate cancer screening or for discriminating between prostate cancer and prostate hyperplasia for patients with high PSA levels.

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Kalberer Christian | **Immunotherapy with mega doses of activated natural killer cells in haematopoietic malignancies and follow-up analysis of *in vivo* cell migration and survival** (KLS 3190-02-2013)
Duration: 01.01.2014 – 31.12.2015

Acute myeloid leukaemias (AML) are rapidly-progressing blood cell malignancies with poor prognosis. Front-line high dose chemotherapy and allogeneic stem cell transplantation (HSCT) offer the best chance of cure, but relapses are frequent and often fatal. Improved outcome of haploidentical HSCT has been attributed to the graft-versus-leukaemia effect of alloreactive natural killer (NK) cells. It is now established that NK cells have a unique capacity to exert potent graft-versus-tumour effects not only in AML but also in multiple myeloma (MM).

The specific aims of this study are: (1) Two clinical studies to assess feasibility and safety of infusions of expanded haploidentical NK cells in patients with AML and MM after HSCT. NK cells are processed in the newly built good manufacturing practice (GMP) clean room facility of the Diagnostic Haematology Laboratory. The NK cell expansion protocol yields cellular products with high numbers needed for multiple mega dose NK-DLIs to achieve clinically relevant effector to target ratios *in vivo*. (2) Characterization of NK cell products to correlate the treatment outcome with NK cell dose, timing and properties. We will monitor survival of infused NK cells in blood and analyse their chemokine receptors expression pattern for a better understanding of NK cells' migration patterns. The goal of this study is to advance immunotherapeutic NK cell trials by developing clinically-suitable approaches to increase the cure rate of patients with AML and MM.

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Krenger Werner | **Role of sphingosine-1-phosphate (S1P) receptor agonism in engraftment, T-cell regeneration, and anti-tumour immunity in preclinical and clinical haematopoietic stem cell transplantation**
(KFS 3237-08-2013)
Duration: 01.03.2014 – 29.02.2016

The combination of radiotherapy, chemotherapy and allogeneic hematopoietic stem cell transplantation (allo-HSCT) is an important treatment option for blood cancers such as leukaemia and lymphoma. One major complication after allo-HSCT is graft-versus-host-disease (GvHD), which occurs in up to 50 % of all patients. GvHD is induced by donor T-cells contained in the transplant, attacking recipient tissues in skin, liver and gastrointestinal tract. Currently, there is no effective treatment for GvHD apart from immunosuppressive drugs, which also enhance the risk for infections.

Our research targets a successful inhibition of T-cell migration into target tissue. Sphingosin-1-phosphate receptor (S1PR) is known to be crucial for T-cell trafficking. A modified S1PR agonist can interfere with cell trafficking and may thus avoid target organ damage. Using mouse models of GvHD we aim to investigate the impact of S1P receptor agonism on anti-tumour immunity, T-cell regeneration and stem cell engraftment. These results will provide important knowledge about the clinical potential of S1P agonist and aid the designing of future clinical trials that might introduce S1P agonist to prevent GvHD while maintaining anti-tumour immunity.

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Kruithof Egbert | **Regulation of procoagulant activities of acute promyelocytic leukaemia cells**
(KFS 3163-02-2013)
Duration: 01.10.2013 – 30.09.2014

Acute promyelocytic leukaemia (APL) is associated with severe bleeding complications. Production of a pro-thrombotic factor by the leukaemia cells leads to the formation of blood clots. In reaction, endothelial cells, which surround the blood vessels, release an anti-thrombotic factor that stimulates thrombus degradation. Together these pro- and anti-thrombotic activities are responsible for an exhaustion of blood coagulation factors, which increases the risk of bleeding. Mortality used to be very high in APL, but since the introduction of therapy with retinoic acid, survival prognosis is relatively good. Nevertheless, severe bleeding remains one of the principal complications, even with optimal therapy.

We will use APL cells as a model to better investigate the mechanisms that regulate the production of pro-thrombotic factors of these leukaemia cells. The knowledge that we hope to gain may be relevant not only for acute promyelocytic leukaemia but also for other types of leukaemia and solid tumours where thrombotic complications are frequent.

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Langer Rupert | **The impact of autophagy on biology and chemoresistance of oesophageal adenocarcinomas** (KFS 3083-02-2013)
Duration: 01.06.2013 – 31.05.2015

Oesophageal adenocarcinomas (EAC) are highly aggressive tumours showing considerable rates of resistance to conventional cytotoxic treatment. EAC represent the 7th leading cause of cancer related deaths in the Western world, and incidence is increasing. The underlying reasons for chemoresistance of a subset of EAC are still not fully understood, and there is also a lack of appropriate tools for pre-therapeutic response prediction or strategies to overcome chemoresistance.

We aim to determine the role of autophagy (self-digestion), a molecular mechanism that helps to maintain cellular homeostasis, in EAC with a special emphasis on chemotherapy response. We are combining cell line experiments with molecular genetic analysis of molecules in tissue of EAC. The current therapeutic approach for the treatment of advanced EAC offers a valuable model for studying therapy effects by comparing molecular signatures of tumours before and after treatment. These analyses are paralleled by laboratory experiments, where cell lines are treated likewise. We aim at obtaining novel insights into the impact of this highly interesting cellular mechanism in cancer.

We hope that we will be able to identify autophagy-related molecules as potentially useful prognostic or predictive biomarkers for the use in clinical practice. The results of our study may offer a valuable contribution for the understanding of cancer biology, chemotherapy resistance and response.

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Lugli Alessandro | **MicroRNAs in the tumour microenvironment of colorectal cancer: novel targets for therapeutic intervention?** (KFS 3294-08-2013)
Duration: 01.01.2014 – 31.12.2015

The tumour microenvironment of colorectal cancer (CRC) is the frontline of tumour-host interaction. Infiltration by T-effector lymphocytes is characteristic of an active anti-tumoural immune defence by the host. In contrast, presence of dissociated tumour cells at the invasive front of CRC ("tumour budding") is a central hallmark of aggressive disease biology and is related to the process of epithelial-mesenchymal transition (EMT). These features represent diametrically opposed sides of an attacker/defender model. Recent studies indicate that the composition of the tumour microenvironment is a central histomorphological prognostic factor and influences therapy response of CRC patients. We hypothesize that the balance of pro- and anti-tumoural factors could be significantly influenced through the expression of short, non-coding, highly conserved RNA-oligonucleotides (microRNA).

In this study, microRNA expression and the composition of the tumour microenvironment is investigated in a well-characterized cohort of CRC patients using the newly developed next generation tissue microarray (ngTMA) technology. The aim of the first part of our study is to identify prognostically relevant microRNAs in the tumour microenvironment of CRC and to study their impact on EMT and tumour immune rejection. In the second part of our investigation, functional analyses and therapeutic targeting of specific microRNAs will be performed using cell biology methods and murine models.

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Matter Matthias | **Identification of mechanisms that promote liver cancer** (KFS 3302-08-2013)
Duration: 01.05.2014 – 30.04.2017

Hepatocellular carcinoma (HCC) is the third leading cause of cancer related deaths and the fifth most common cancer in the world, with a fast growing incidence in the United States and Europe. Most HCCs develop in the context of a chronic liver inflammation, mainly due to chronic infection with hepatitis C or B virus or alcoholic and non-alcoholic steatohepatitis. Chronic liver inflammation causes tissue damage with liver cirrhosis and creates a microenvironment that favours the development of HCC.

Currently, little is known about why certain patients with cirrhosis develop HCC, whereas others do not. Clearly missing in the field of HCC research are longitudinal studies that analyse the changes occurring in the liver over the years up to HCC development in the same patient. In our project, we will therefore analyse liver tissue samples from patients at two different points in time: one when no HCC was present and one when a HCC was present.

We will perform an array-based whole genome RNA expression analysis to investigate the changes occurring between these two liver samples. We will analyse liver tissue samples in a control group of cirrhotic tumour-free patients who have not developed a HCC in a defined time period. Our analysis will help design treatment options for the prevention of HCC and improve our understanding of the mechanisms involved in HCC development.

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Mazzucchelli Luca | **MYC activation in diffuse large B-cell lymphomas** (KFS 3266-08-2013)
Duration: 01.02.2014 – 31.01.2017

Diffuse large B-cell lymphoma (DLBCL) is the most frequent aggressive B-cell lymphoma in adults. Up to 40 % of treated patients have refractory disease or relapse. Despite several efforts over the recent years, the molecular basis of DLBCL remains largely unclear, and few results have attained clinical relevance.

This incomplete success reflects the heterogeneity of DLBCL and the poor understanding of its pathogenesis. One of the most important pathogenic features in DLBCL is activation of the MYC oncogene, which can be caused by several mechanisms and leads to aggressive behaviour. For this reason, characterization of MYC target genes in DLBCL and of their downstream effectors represents a crucial step in the understanding and prevention of lymphomagenesis.

The aim of the research project is therefore to analyse the prognostic impact of the genetic alterations of MYC, as well as of its expression levels, in a large series of patients with DLBCL, with well characterized follow-up information. Further, we intend to study the role of MYC activation on two recently discovered proteins, PIM1 and STAT3, known to play a major role in regulation of MYC expression. Finally, we will analyse the expression of BRD4 and TTP in a series of DLBCL, as these proteins were shown to represent two potential therapeutic targets in haematologic neoplasms characterized by MYC activation.

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Nadal David | **Translational research with the goal to identify, characterize, and target B-ALL-specific and Burkitt's lymphoma-specific T-helper cells**
(KLS 3189-02-2013)
Duration: 01.09.2014 – 30.08.2016

Acute lymphoblastic leukaemia (ALL) represents the leading cause of cancer related deaths in children and young adults. Although modern treatment has reached an excellent rate of success, about 20 % of the patients relapse, and side effects remain a problem. Similarly, intensive chemotherapy has reached excellent cure rate in children with Burkitt's lymphoma (BL), but patients suffer from severe side effects. There is a need for less toxic and more targeted therapies. Cancer cells (B-ALL cells and BL cells) grow and expand in the patients' bone marrow and organs, where they interact with surrounding cells, such as T-helper cells. The influence of these T-helper cells on B-ALL or BL cells is not known so far.

In this project, we will investigate the role of T-helper cells in B-ALL and BL disease development. To do so, the lymphoma-interacting T-helper cells will be isolated from patients and cultured together with B-ALL and BL cells from the same patient. In this way, we will analyse whether these T-helper cells can kill the tumour cells, or whether they in contrast help the malignant cells to survive and/or expand. Further, we will analyse the mechanisms that are involved in the interaction of T-helper cells with B-ALL and BL cells. The question as to whether T-helper cells promote lymphoma and leukaemia growth is highly relevant for future therapies, which might involve specific removal of disease-promoting T-helper cells. In addition, the project may identify molecules involved in this interaction. Future cancer therapies may involve blocking such molecules.

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Petrausch Ulf | **Phase I study for the adoptive transfer of re-directed FAP-specific T-cells in the pleural effusion of patients with malignant pleural mesothelioma** (KFS 3115-02-2013)
Duration 01.10.2013 – 30.09.2015

T-cells are effector cells of the immune system and constantly scan the body for malignant transformation of cells. If malignant transformation is detected, the transformed cells are destroyed. However, the process of malignant transformation also includes processes by which the malignant cells escape T-cell recognition and tumour formation occurs. As part of this clinical phase I study protocol, T-cells from patients with malignant pleural mesothelioma (MPM) will be isolated and reprogrammed to detect the fibroblast activation protein (FAP) on the tumour cell surface. Today, MPM is an incurable disease for which new therapeutic approaches have to be developed.

The target antigen FAP is highly expressed on MPM cells. The reprogrammed T-cells from the patients will receive by gene transfer a new receptor recognizing FAP. When the receptor binds to the FAP molecule on MPM cells, T-cells will become activated and kill the tumour cells specifically. To optimize the efficacy of the approach, T-cells will be injected into the thoracic cavity to allow for rapid contact of the T-cells with the tumour cells. Patients included in this trial might not have an immediate therapeutic effect, since the first T-cell dose administered will be quite low. However, the low dose is necessary, because this is the first application of FAP-specific T-cells in humans. We believe that the trial will generate new knowledge in the field of adoptive T-cell transfer.

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Rechsteiner Markus | **Non-invasive identification of VHL mutations in plasma by deep-sequencing with subsequent assessment of mutant pVHL functionality in FFPE by FRET-FLIM in ccRCC patients**
(KLS 3123-02-2013)
Duration: 01. 07. 2013 – 30. 06. 2014

Renal cell carcinoma (RCC) is the most frequent malignant tumour affecting the adult kidney, and its manifestation is often asymptomatic in its early phase. Characteristic for the majority of ccRCC is the functional loss of the von Hippel-Lindau (VHL) tumour suppressor gene. Up to now, no non-invasive tool is available to determine the mutation status of VHL. Therefore, the first aim of this project is to establish a method to isolate tumour DNA, which is present in smallest amounts in the blood. The VHL mutation status can then be assessed by a new technology, called ultra-deep-sequencing.

The common mutations of VHL in ccRCC led to its in-depth characterization, which revealed its function as a multiadapter protein, in particular its interaction with the hypoxia-inducible factor (HIF). HIF is involved in i. e. the regulation of tumour angiogenesis, which may be inhibited by targeted therapy. To select the patient population that benefits the most from such a therapy, not only the mutation status of VHL is important to know but also whether it has lost its functionality. Therefore, we aim in this project additionally to establish a FRET assay that can measure the binding differences from non-mutated and mutated pVHL to HIF . The ultimate goal of this project is to integrate ultra-deep-sequencing and FRET technology as identification and monitoring tools of ccRCC in clinical diagnostics.

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Reyes Mauricio | **Medical image analysis for brain tumour studies** (KLS 3167-02-2013)
Duration: 01.08.2013 – 31. 07. 2015

Brain tumours are rare but have a limited survival rate. Magnetic resonance imaging (MRI) is the method of choice in diagnosis, treatment and follow-up of brain tumours. Currently, tumour size and growth assessment is performed visually by experienced radiologists using diameter measurements. Automatic methods for analysing brain tumour images volumetrically would facilitate and accelerate the clinical workflow. At the same time, this can have a positive impact on therapy. Previously, we developed software tools for automatic segmentation of tumour sub-compartments as well as healthy tissues.

The aim of this project is to consolidate previous developments and transform the tools into a clinical application. For this, we want to integrate the tools into a clinically-oriented graphical user interface for thorough evaluation and validation in a clinical study that is carried out together with our clinical partners. Based on the results of the study and feedback from the physicians, detailed improvements will be made. This suite of tools has the potential to significantly ease the burden of image analysis work currently posed on radiologists and will benefit patients by providing more accurate and objective interpretation of the disease.

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Rottenburger Christof | **^{177}Lu-PP-F11N for receptor-targeted therapy and imaging (theranostics) of metastatic medullary thyroid cancer: a pilot and a phase I study** (KFS 3170-02-2013)
Duration: 01. 07. 2014 – 30. 06. 2017

Today, patients with advanced medullary thyroid carcinoma who do not have the option of curative surgery have very limited treatment options, as chemotherapy or external beam radiotherapy are not effective enough. Novel substances (called multikinase inhibitors) are now available for the treatment of medullary thyroid cancer. However, they have not improved survival of these patients. Unfortunately, these multikinase inhibitors can have adverse effects that impact quality of life.

Often the tumour marker calcitonin is increased in these patients, indicating residual or recurrent tumour disease. Frequently, the residual or recurrent tumour cannot be found with conventional imaging such as CT or MRI. Scientific studies have shown that almost all medullary thyroid carcinomas express the gastrin receptor at a high density on the cell surface. Therefore, peptides that bind to the gastrin receptor were designed and labelled with radionuclides. These substances have been improved recently and are now available for imaging and therapy studies in patients with medullary thyroid carcinomas. We are investigating whether these new substances are useful for imaging and therapy of advanced medullary thyroid cancer. Further, we will determine the maximal treatment dose that is safe and effective in patients.

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Fotogramm / Zickzack, 2013

Simon Hans-Uwe | **Characterization of ATG5 as a tumour suppressor in cutaneous melanoma**
(KFS 3099-02-2013)
Duration: 01. 07. 2013 – 30. 06. 2015

Cells require the removal of damaged proteins and organelles to stay healthy. This renovation process is performed by intracellular digestion of cytosolic material, which is called autophagy. There is evidence that insufficient autophagy contributes to cancer, but the molecular mechanisms remain largely unclear. We hypothesize that the expression of genes regulating autophagy is dysregulated in cancer. In this project, we are investigating the expression and function of autophagy-regulating genes in melanoma patients.

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Tausch Christoph | **Randomized controlled trial to evaluate the impact of a surgical sealing patch on lymphatic drainage after axillary lymph node dissection for breast cancer** (KFS 3300-08-2013)
Duration: 01. 10. 2014 – 30. 09. 2016

This study is based on the use of the local haemostyptic and sealing surgical patch TachoSil®. A meta-analysis of 11 randomized controlled trials with 632 patients showed no impact of the use of fibrin glues after axillary lymph node dissection (ALND) on the risk of seroma or the length of hospital stay but revealed a trend toward less drainage volume. In all of the studies, the liquid form of fibrin sealant was used.

TachoSil® is a sterile, ready-to-use, absorbable surgical patch – as opposed to the liquid fibrin sealant mentioned above, and it consists of an equine collagen sponge coated with human fibrinogen and human thrombin. TachoSil® was launched in Europe in 2004 as a further development of the TachoComb® and TachoComb H® products, which have been used in more than 1.7 million patients in over 20 different countries in a wide range of surgeries since their introduction in the early 1990s. TachoSil® is used not only for haemostasis but also for closure of other anatom-

ical structures in many surgical disciplines due to its excellent sealing capacity. The use of TachoSil® has been shown to reduce the lymphatic drainage after lymphadenectomy in several indications.

We propose to conduct a multicentre prospective randomized clinical trial in Switzerland to evaluate the impact of TachoSil® on axillary drainage after ALND for breast cancer. We hypothesize that the use of TachoSil® significantly and relevantly reduces the volume and duration of axillary drainage after ALND. This is likely to affect patient safety and to decrease the length of hospital stay as well as hospital costs, and it has the potential to banish the axillary drain from clinical routine in the future.

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Theocharides Alexandre | **The CD47-SIRPα interaction and the role of ikaros in myeloproliferative neoplasms** (KFS 3298-08-2013)
Duration: 01.10.2013 – 30.09.2016

Myeloproliferative neoplasms (MPN) are a group of blood stem cell disorders characterized by increased production of blood cells. Therapy-resistance and development of acute leukaemia (post-MPN-AML) are two of the most important complications in MPN that significantly impact survival. Macrophages are cells of the innate immune system that can eliminate cancer cells. This study aims at elucidating the role of an interaction between macrophages and MPN cells and at developing a therapy model for post-MPN-AML. Cancer cells carry proteins on their surface that mediate interactions with macrophages and prevent them from being eliminated.

We will assess whether blocking these interactions by a novel therapeutic strategy leads to elimination of MPN cells by macrophages. To model post-MPN-AML, human blood cells will be genetically modified with genes known to be involved in leukaemia initiation. Genetically modified cells will be exposed to a panel of therapeutic compounds in tissue cultures to identify the one with the greatest therapeutic potential. The same cells will then be transplanted into a mouse model, and mice will be treated with the most promising compound selected from the tissue culture experiments. The proposed model will constitute a highly valuable tool to assess efficacy of novel agents and to set the stage for a clinical trial with the most promising therapeutic regimen for post-MPN-AML.

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Tornillo Luigi | **Understanding the molecular mechanisms of differential responses to anti-angiogenic treatment in colorectal cancer** (KFS 3169-02-2013)
Duration: 05.01.2013 – 30.04.2016

Despite improvements in surgical and pharmacological therapies, the 5-year survival rate for advanced stage colorectal cancer (CRC) is about 10 %. Although the recent introduction in treatment of an antibody (bevacizumab, BV) that targets the product of a gene named VEGFA doubled the survival expectancy of patients with CRC, the results are still rather poor compared to other cancers, and the response to BV in the individual patient remains unpredictable.

We found that amplification of the VEGFA genes identifies a subset of patients with CRC with highly aggressive disease who probably respond better to BV treatment than patients without gene amplification. At present, however, we do not know the molecular mechanism underlying our data. We therefore aim to unravel the BV mechanisms of action, by using an animal model recapitulating the human disease, and to investigate how VEGFA gene and its family members modulate patients' response to BV treatment.

Altogether, our study will help the setting of personalized therapeutic strategies by: (1) helping to identify those patients who most probably will profit from BV treatment; (2) avoiding unnecessary side effects and costs for nonresponders; and (3) planning future alternative and/or combination treatments for patients with CRC based on the functional results obtained. We believe that patients with CRC will greatly benefit from these research activities.

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von der Weid Nicolas | **Effects of a 1-year partially supervised exercise programme in childhood cancer survivors: a randomized controlled trial** (KLS 3175-02-2013)
Duration: 01.01.2014 – 31.12.2016

Exercise can play a major role in mitigating or even preventing diverse late effects in cancer survivors, such as cardiovascular disease, obesity, osteoporosis and reduced quality of life. The objective of this study is to assess the effect of an exercise programme of one year's duration on cardiovascular health, obesity, osteoporosis, mental health and quality of life in childhood cancer survivors.

We will recruit survivors aged 16 years and older from the paediatric oncology clinic at Children's Hospital Basel and randomize them into an intervention and a control group after stratification for type of tumour and therapy. The intervention group will be asked to increase their physical activity for one year by at least three hours of intense physical activity weekly and reduce screen time by 25 %. Regular feedback will be given via a step counter, an online activity diary, and by the centre staff. The control group participants will keep their activity level constant.

All participants will be seen after three, six and 12 months to assess health and quality of life parameters. After one year, the control group will be given the opportunity to receive the same intervention to profit from an active lifestyle.

Should the program prove effective, a complete package will become available to all paediatric oncology centres in Switzerland to promote exercise in childhood cancer survivors.

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von Gunten Stephan | **Siglec-7/-9 ligand receptor interactions in NK cell-mediated tumour immunosurveillance** (KFS 3248-08-2013)
Duration: 01.02.2014 – 31.01.2017

Altered surface glycosylation (presence of carbohydrate residues) on malignant cells may directly influence immune responses by interaction with receptors on immune cells. By this means tumour cells are protected from the immune response by natural killer (NK) cells by interacting with inhibitory Siglec-7 and -9 receptors. In this study we are investigating the stage-dependent expression of carbohydrate ligands for Siglec-7 and -9 in different types of cancer. The role in tumour defence of specific Siglec-7- or -9-positive NK cell subsets will be investigated. Further, we will explore the extent to which overexpression of Siglec-7 and -9 ligands protects against NK cell-mediated defence, and whether interference of Siglec ligand receptor interactions restores or enhances NK cell-mediated immunosurveillance of NK cell-resistant or -sensitive tumours.

Mechanistic studies will uncover a potential role of Siglec-7 and -9 receptors in the formation of the NK cell immunological synapse, the site of contact between NK cell and the targeted tumour cell. The experiments will provide further insights into the role of Siglec receptor ligand expression and interactions in different types of malignancies and might lead to novel diagnostic or prognostic biomarkers and molecular targets for therapeutic intervention in cancer.

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Zajac Paul | **Investigator-initiated phase I immunotherapy trial for patients bearing non-small cell lung cancers expressing cancer/testis tumour antigens and treated with a non-replicating vaccinia virus encoding for 7 antigenic epitopes, CD80 and CD154 co-stimulatory molecules** (KFS 3149-02-2013)
Duration: 01.05.2013 – 30.04.2015

Recent clinical developments have finally led to recognition of immunotherapy as a major approach to treatment of cancer. In this framework, the objective of our phase I/II clinical study is to validate a new generation cancer vaccine, notably for patients with lung cancer. The vaccine consists of an inactivated (non-replicating) viral vector expressing seven tumour antigen epitopes stimulating specific cytolytic immune responses against tumour cells. Moreover, the vaccine expresses two immune stimulatory molecules, CD80 and CD40 ligand, which significantly improve the quantitative and qualitative activation of cytotoxic T-lymphocyte. Targeting the "cancer/testis antigens" allows the generation of immune responses specific against tumour cells, and the multiplicity of targeted antigens limits the frequent "tumour escape" that is observed in mono-antigen therapies.

Following surgical tumour resection and post-op standard of care, selected patients with cancer will receive a total of eight intradermal vaccinations during a period of one year. The primary objective of this phase I study is the vaccine safety demonstration for the patient. But the secondary objectives of immunological and clinical efficacy will also be carefully followed and analysed.

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Web-based psychological support for people with cancer

For most people, a cancer diagnosis means an existential life crisis. The disease and the medical treatments bring many physical, emotional, and social stresses and strains. When people learn that they have cancer, complex emotional/mental processing begins that can lead to a temporary stress response and, for approximately 30 % of patients, to a mental disorder (most frequently adjustment disorders in response to the new life event, depression, and anxiety disorders).[1] Depressive disorders and anxiety disorders have, among other things, a negative effect on quality of life, treatment compliance, health behaviour, and decision making.[2] Many patients with cancer deal with the challenges that cancer brings by themselves or with support from their social network. But more than half of all persons with cancer demonstrate a need for psychosocial treatment or counselling in the course of the disease.[3]

The overarching goals of psycho-oncological interventions are facilitation of dealing with the disease through the patient developing adequate response and coping strategies, increasing the patient's resources, maintaining or improving quality of life, and treating emotional stress responses in patients and also in their family members. The effectiveness of psycho-oncological interventions in reducing emotional and stress reactions, improving quality of life, and coping with side effects has been well researched and is supported by the evidence.[4]

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The National Cancer Programme for Switzerland 2011–2015 (NCP II) and, based on that, the "National Strategy Against Cancer 2014–2017" (NSC) aim in particular to create better connections between existing psycho-oncological services and oncological health care and to make the treatment/counselling options available to everyone. In addition, the services are to be low-threshold as well as time- and cost efficient.

To meet these goals, the question arises as to whether psycho-oncological care, which takes place in direct contact with the patients, can be usefully complemented by web-based counselling and treatment options. Studies in other countries have found that web-based options that contain interactive elements (for example, with symptom monitoring or in the form of practice exercises) as well as regular feedback from and contacts with a psycho-oncology specialist are more effective than purely self-help programmes.[5,6]

Online research in the field of psycho-oncology has only just begun in Switzerland. In the following, we present three ongoing research projects, each with a different focus, in which web-based counselling and treatment options are being developed for different patient groups and their usefulness and potential for psycho-oncological care in Switzerland investigated.

STREAM: A web-based stress management programme for patients with a new cancer diagnosis

The aim of this new Internet-based stress management programme is to help patients newly diagnosed with cancer to cope with their stress. Previous studies showed that stress reduction techniques from behavioural therapy are very effective in reducing stress and improving adjustment to the disease. A first online stress management intervention was found to improve participants' coping with their cancer.[7] The STREAM *(Stress aktiv mindern)* project, funded by the Swiss Cancer Research foundation and the Swiss National Science Foundation, is testing the feasibility, practicability, and effectiveness of a web-based intervention. All that is required of patients is that they have basic skills in using the Internet and computers and good knowledge of German. The STREAM project is examining what groups (age, gender, and type of cancer) make use of this kind of psycho-oncological care and for how long and to what extent. To test the effectiveness of the programme, the participants are being surveyed on stress and their quality of life.

The stress management intervention is based on elements of cognitive behavioural therapy and on mindfulness- and acceptance-oriented techniques. It was developed by psychologists at University Hospital Basel and Bern University Hospital with the assistance of oncologists. The programme contains eight chapters on understanding stress and the effects of stress at the cognitive, emotional, and physical levels. With the help of interactive elements, participants are meant to learn and practice coping strategies and mobilize resources. Each chapter begins with an information section followed by a self-observation part and a part with practice exercises. Patients work through the programme contents on their own and in a specified order. Regular contacts with the psychologists on the study team take place weekly by

e-mail. After completing the programme, the participants are free to continue to use the contents.

All of the exercise materials such as audio files and instructions to the exercises are available on the website at *www.stress-aktiv-mindern.ch*. The online portal is divided into a public area with general information on the stress management programme and contact and sign-up information. The password-protected area is only accessible by study participants. For further information on the programme and the research study, e-mail *stream@usb.ch*.

FAMOCA: Web-based psycho-oncological support for families with parental cancer

A cancer diagnosis of a parent is a great challenge for the whole family, and it can change family stability, relationships within the family, and quality of life. About 25 % to 30 % of partners and children of a parent with cancer develop clinically relevant levels of psychological symptoms. Up to now, there have been only few preventive interventions and treatment approaches that include the whole family, because it is often difficult to bring all family members together at one place and time. Here, the Internet offers a new and cost-effective possibility, as it can be used by several persons independently of time and location.

Funded by the Swiss Cancer Research foundation, the FAMOCA (Family online counselling for families with parental cancer) project is being conducted by University Hospital Basel, Child and Adolescent Psychiatry Baselland, and the University of Basel. The project is investigating what help a web-based counselling programme for families affected by parental cancer can offer for dealing with the disease and is evaluating the programme's effectiveness. The website *www.famoca.ch* has separate areas for parents, young people aged 12 to 18 years, and children aged 3 to 11. Thanks to this division, information and suggestions for promoting family communication and for developing and practising coping strategies can be provided at the individual, couple, and family level age-specifically. The aim is to improve the family members' adjustment to the disease. The programme contains four chapters, which are provided at monthly intervals. Children can work on the contents by themselves or in the company of a parent. Various elements are available also in audio format.

The online portal has a public area providing general information on the programme and contact and sign-up information. The password-protected can be accessed only by families that are participating in the study. For further information on the programme and the research study, e-mail *info@famoca.ch*.

Online decision-aid tool for young women with cancer

Successful cancer treatment can lead to a temporary or lasting reduction of fertility, which can have serious consequences for the later quality of life of young women with cancer. Today, various fertility preservation options are available in part established methods like embryo (fertilized egg) freezing, in part still largely experimental methods like removal and freezing of ovarian tissue. If they want to choose one of these options, young women have to make their decision within the short period of time between cancer diagnosis and the start of treatment, which is stressful in an already stressful time. This situation is a challenge for both patients and their families and the health care team. Several studies have shown that for young women with cancer later fertility is very important, but they have insufficient knowledge of the fertility preservation options. And later on, some patients do not even remember having ever been informed about these options.

To optimize counselling in such situations, a group of researchers in Australia developed a decision aid in the form of a brochure. The researchers found that thanks to the information and the worksheets, the patients participating in the study felt that they had less decisional conflict, were better informed, and regretted their decision one year later less frequently than women who been advised in the customary way.[8] These results show that a standardized instrument that complements the usual advising has a positive effect on the decision-making process. Computer and Internet are young patients' preferred communication medium. Based on these results, a research team at the Department of Obstetrics and Gynaecology at University Hospital Basel developed a web-based decision-aid tool concerning fertility preservation options.

The research project, which won the *Swiss Bridge Award* 2013, encompasses both the development and the evaluation of the decision-aid tool. The evaluation is being conducted in collaboration with other centres for reproductive medicine in Switzerland that perform fertility-preserving procedures. The study, titled "Decisional conflict of young cancer patients with regard to fertility preservation – effects of an online decision-aid tool", seeks answers to the following questions: Can the decision-making process be supported and made easier? Can patients' knowledge of fertility preservation options be improved? Can decisional conflict be significantly reduced? Will the web-based decision-aid tool result in less frequent regret about the decision made?

One group of participants will receive the advising that is standard practice today and will be compared to a group of patients that in addition to the usual advising will be able to use the online tool. To measure the amount of decisional conflict and how much the decision may be regretted, validated questionnaires are available. If the web-based tool proves to be valuable, the plan is to make it available in the future to all young women with cancer diagnoses whose treatment could result in infertility.

The three projects described here illustrate how web-based support instruments could complement psycho-oncological treatment offerings in Switzerland. How much benefit they provide to patients will be seen in the next few years. Whether this type of support should be further pursued will depend on that.

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Sibil Tschudin is a specialist in obstetrics and gynaecology with sub-specialties in psychosomatic and psychosocial medicine and sexual medicine. She has headed the Division of Gynaecological Social Medicine and Psychosomatics at the Department of Obstetrics and Gynaecology of University Hospital Basel since 2008. Her clinical work includes counselling and care in the areas of sexuality and contraception, infertility, prenatal diagnostics, and premenstrual syndrome. Her current research focuses on psychological aspects of fertility preservation measures for young women with cancer.

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PD Judith Alder, PhD

Judith Alder studied psychology at the University of Basel. After completing her doctoral degree she worked as head psychologist at University Hospital Basel, where she completed a habilitation (qualification as a university lecturer) in gynaecological behavioural medicine in 2008. Since 2013 she has worked as a psychotherapist and psycho-oncologist in her own practice in Basel. She is currently participating in web-based research projects in psycho-oncology and obstetrics.

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Completed research project in 2013

Burton-Jeangros Claudine | KFS 2816-08-2011 | CHF 80,800.–
Département de sociologie, Université de Genève, Genève
Women's views on cervical cancer screening. A qualitative study of barriers to screening and HPV self-sampling acceptability

Presentation of completed research project in 2013

Burton-Jeangros Claudine | **Women's views on cervical cancer screening: a qualitative study of barriers to screening and HPV self-sampling acceptability**
(KFS 2816-08-2011)

Social science studies have identified several obstacles to cervical cancer screening, including barriers related to information, and emotional and practical barriers. It is expected that HPV self-sampling procedures could reduce some of these barriers.

Aim

This study aims at describing women's views on cervical cancer screening, assessing the different obstacles that restrict participation in screening and evaluating the benefits and disadvantages of HPV self-sampling.

Method

We conducted 24 focus groups with a total of 125 participants, aged between 24 and 67, in the French-speaking part of Switzerland in 2012.

Results

Participants confirmed that various difficulties concerning getting screened arise; rather than one single factor explaining non-attendance, a constellation of barriers may deter women from attending screening. These factors relate to different aspects of the Pap smear procedure, including gaps in information, reluctance or difficulty to see a gynaecologist, and uneasiness associated with the pelvic examination. Gaps in knowledge were not specific to particular subgroups of the participants and were observed for Swiss and migrant women, women with a professional education and women having attended university, and young and older participants. Barriers are also related to the social life of these women: Some life stages are more (pregnancy) or less (absence of sexual activity) conducive to seeing a gynaecologist for prevention reasons. Participants saw some advantages in HPV self-sampling, but they also expressed concerns regarding their ability to perform the test in an adequate manner.

Recommendations

In the Swiss opportunistic system, some important gaps in information related to cervical cancer screening exist. Therefore, it is particularly important to improve the information level in the whole population. Furthermore, the study highlighted the importance of the context in which screening takes place and makes gynaecologists aware of the difficulties expressed by women, which could contribute towards improving screening participation.

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List of approved research projects in 2013

Total funds allocated: CHF 985,700.–

Baumgartner Edgar | KFS 3112-02-2013 | CHF 150,000.–
Hochschule für Soziale Arbeit, Fachhochschule Nordwestschweiz, Olten
The effect of social counselling services on quality of life and coping with burden of parents of a child with cancer: a randomized intervention study at the University Paediatric Clinic Zurich

Eicher Manuela | KFS 3269-08-2013 | CHF 34,400.–
Recherche & développement, Haute école de santé Fribourg, Fribourg
Testing the feasibility of an integrated care model in ambulatory oncology furthering resilience in patients with gastrointestinal and lung cancer: a phase II trial (GI & LUNG RESIL-Trial)

Rüesch Peter | KFS 3258-08-2013 | CHF 148,700.–
Fachstelle Gesundheitswissenschaften, Departement Gesundheit, Zürcher Hochschule für Angewandte Wissenschaften (ZHAW), Winterthur
Prostate cancer e-health tutorial (PROCET)

Senn Beate | KFS 3160-02-2013 | CHF 164,000.–
Institut für Angewandte Pflegewissenschaft, Hochschule für Angewandte Wissenschaften, St. Gallen
The impact of the self-management intervention "WOMAN-PRO II programme" on patients with vulvar neoplasia to minimize post-surgical symptom prevalence: a mixed-methods project

Urech Corinne | KFS 3260-08-2013 | CHF 252,300.–
Gynäkologische Sozialmedizin und Psychosomatik, Frauenklinik, Universitätsspital Basel, Basel
Web-based stress management for newly diagnosed cancer patients (STREAM-1): a randomized, wait-list controlled intervention study

Zwahlen Diana | KLS 3186-02-2013 | CHF 236,300.–
Abteilung Psychosomatik, Universitätsspital Basel, Basel
Understanding why cancer patients accept or turn down psycho-oncological support. A prospective observational study including patients' and clinicians' perspective on communication about distress

Presentation of approved research projects in 2013

Baumgartner Edgar | **The effect of social counselling services on quality of life and coping with burden of parents of a child with cancer: a randomized intervention study at the University Paediatric Clinic Zurich** (KFS 3112-02-2013)
Duration: 01.12.2013 – 30.11.2016

Childhood cancer often leads to acute psychosocial burden for the child and the whole family. After the shock of the diagnosis and the subsequent necessity for the entire family system to learn to deal emotionally with diagnosis and prognosis, there is often a difficult phase of adaptation to restrictions in life conduct due to the treatment regime. This is where social counselling offers professional support: it makes possible active life conduct and coping with everyday life with the goal to improve or at least stabilize the quality of life of families. However, little is known about the effect of this kind of clinical social work practice.

This randomized intervention study at the University Paediatric Clinic Zurich aims to investigate whether social counselling can support the life conduct of families and deal with problematic dynamics successfully and effectively. Further, different methods of social diagnosis will be applied to explore the need for support services. The investigation of the effects of these different methods will provide a basis for targeted allocation of limited counselling resources.

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Eicher Manuela | **Testing the feasibility of an integrated care model in ambulatory oncology furthering resilience in patients with gastrointestinal and lung cancer: a phase II trial (GI & LUNG RESIL-Trial)** (KFS 3269-08-2013)
Duration: 15.11.2013 – 14.09.2015

Besides the importance of cancer survival, health professionals involved in cancer care increasingly recognize the value of considering how well people live with and after cancer. Psychosocial care that mainly aims at relieving emotional distress and promoting well-being is a central element in improving the quality of patients' lives. Many people with gastrointestinal and lung cancer who could benefit from psychosocial care do not receive it. This might negatively impact their return to an active life. To improve the psychosocial care of patients with gastrointestinal and lung cancer, we developed an integrated care model furthering resilience and thereby improving supportive care.

The aim of this study is to test if this intervention provided by nurses and oncologists is feasible within the real life context of an ambulatory oncology clinic, and to find out what the ideal intensity of such an intervention is. Patients willing to participate in the study will be randomly allocated into two groups. In both groups patients will be invited to fill out questionnaires on resilience, their perceived unmet supportive care needs, their general mood, perceived quality of life and coping effort. Information on individual resilience level and unmet needs will be synthesized electronically and directly fed back to the oncologists and nurses in charge of the patient. They will receive tailored propositions on how to support patients to meet their needs in a resilience-furthering way. In one group, patients will in addition be supported by two individual nurse consultations provided face-to-face and three consultations provided by telephone. This study will give us new information on how to improve access to psychosocial care for gastrointestinal and lung cancer patients and thereby improve quality of care.

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Rüesch Peter | **Prostate cancer e-health tutorial (PROCET)** (KFS 3258-08-2013)
Duration: 01.04.2014 – 31.03.2017

Prostate cancer is the most common cancer in men, with around 5700 cases and 1300 deaths per year in Switzerland. Men with early-stage prostate cancer are faced with difficult decisions. They are confronted with different treatment alternatives, each with its own benefits and risks. Therefore, comprehensive information provision is very important to facilitate patients' participation in the decision-making process (shared decision-making).

The aim of this project is to develop an e-health tutorial concerning prostate cancer. The e-health tutorial will be developed in a participatory process of technology development. It will then be tested at several urological clinics in the German-speaking part of Switzerland. The tutorial should meet the diverse information needs of patients confronted with early-stage prostate cancer in a comprehensive way by addressing individual information needs. Moreover, it should facilitate the interaction between patients and physicians and reduce decisional conflict with regard to treatment decisions. In addition, general suggestions for setting up an online tool for other cancer-specific and/or health-related issues will be deduced from the findings of this project.

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Fotogramm / Wurmloch, 2013

Senn Beate | **The impact of the self-management intervention "WOMAN-PRO II programme" on patients with vulvar neoplasia to minimize post-surgical symptom prevalence: a mixed-methods project**
(KFS 3160-02-2013)
Duration: 01.09.2013 – 31.08.2016

In pre-cancer/cancer of the external female genital (vulva), surgical interventions cause multiple symptoms that have an impact on women's quality of life and contribute to high health care costs. Patients' symptoms can be reduced by providing adequate treatment. This study aims to compare the impact of standardized care with the WOMAN-PRO II counselling programme regarding the number of post-surgical symptoms in women with vulvar pre-cancer/cancer.

To this purpose, 90 surgically treated patients with vulvar pre-cancer/cancer will be recruited in six hospitals in Switzerland, Austria and Australia. Women will be randomized to standardized care and the WOMAN-PRO II programme. The standardized care group will receive the usual care and a set of informational leaflets during routine medical treatment. The WOMAN-PRO II programme group will receive standardized care, tailored information, motivational interviewing, and strategies to support patient self-management by specially trained gynaecology-oncology nurse specialists during six counselling sessions. Symptom prevalence and secondary outcomes will be collected by means of questionnaires. Additionally, interviews will be conducted with patients and gynaecology-oncology nurse specialists.

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Urech Corinne | **Web-based stress management for newly diagnosed cancer patients (STREAM-1): a randomized, wait-list controlled intervention study** (KFS 3260-08-2013)
Duration: 01.01.2014 – 31.12.2016

About half of patients with cancer suffer from severe stress symptoms, and around one-third of the patients fulfil the criteria for a clinically relevant psychological disorder. It has been demonstrated that psycho-oncological interventions achieve a reduction in levels of anxiety, distress and depression, as well as an increase in quality of life. Still, psycho-oncological support is rarely utilized by male patients and is insufficiently accessible for many patients (i.e. lack of supply in the respective area, cost issues). Web-based psychotherapeutic interventions are a growing field of interest in research, as they can be used independently of time and location and therefore may improve adequate provision of support. However, web-based interventions for cancer patients are still scarce.

This research project will develop a comprehensive stress management programme accessible for a vast number of cancer patients. The study aims primarily to evaluate the feasibility of the programme (technical and organizational feasibility, accessibility). In addition, the preliminary efficacy of the programme will be analysed (by means of changes in levels of stress, anxiety, depression and quality of life). The start of the study or the start of the eight-week programme is 1 June 2014.

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Zwahlen Diana | **Understanding why cancer patients accept or turn down psycho-oncological support: a prospective observational study including patients' and clinicians' perspective on communication about distress** (KLS 3186-02-2013)
Duration: 01.10.2013 – 30.09.2016

One of the objectives of current developments in psycho-oncological care is to introduce routine screening questionnaires for psychosocial distress in order to accurately identify patients in need of psycho-oncological treatment and to ensure that patients have access to supportive care services. The practice has been shown to be effective. However, only a moderate proportion of the distressed patients also accept referrals, and desire for psycho-oncological support is broadly independent of the severity of distress.

In this study we want to better understand: (1) potential predictors of utilization of psycho-oncological service, (2) the reasons given by the patient for (non-)utilization of psycho-oncological support service, and (3) how communication about psychosocial distress and psycho-oncological services on the basis of a short screening questionnaire is perceived by patients and clinicians. This is a prospective observational study. Patients are assessed by telephone interview and with a questionnaire shortly after the first clinical encounter and four months later. Clinicians answer one single questionnaire after the first encounter.

The results may help to adapt routine practices to eliminate barriers to adequate health care and thereby better meet the needs of patients. This investigation will also provide insight into patients' and oncologists' perceptions of discussing psychosocial distress and referral to psycho-oncological support on the basis of a screening questionnaire.

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Fotogramm / Doppelt und umgekehrt, 2012

Cancer survivors: a fast growing segment of the population

The number of people newly diagnosed with cancer has increased over the last 30 years in Switzerland and worldwide. This is the result of higher life expectancies, the growth and the ageing of the population, intensified early detection, and increased public awareness of the disease.[1] Cancer is mainly a disease of the elderly, as two-thirds of cancer cases are diagnosed after age 60. In the same time period, cancer mortality has declined due to earlier diagnosis and more effective treatments, and survival rates have improved.[2,3] The conjunction of these factors has led to a large and rapidly growing number of people diagnosed with cancer during their lifetime.

In Switzerland there are approximately 37,000 new cases of cancer and 16,000 cancer deaths each year.[4] The most frequently diagnosed cancers are breast, prostate, colorectal, lung, skin, and cancer in the haematopoietic system. Cancer is a broad umbrella term covering a multitude of different, complex diseases that differ greatly with regard to their development, course, and treatment.

Cancer survivors: a heterogeneous group

In the English-speaking world, persons living with a cancer diagnosis are called cancer survivors. The number of these persons is called "complete prevalence", which is a measure of the prevalence of cancer in the entire population. Cancer survivors are a heterogeneous group with differing care needs: Whereas some survivors are disease free and only need to be encouraged to have a healthy lifestyle, others struggle with the disease, side effects of treatment, or other consequences sometimes for decades.

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Fotogramm / Tillia, 2013

Consideration of the special needs of cancer survivors

Cancer survivors have greater needs for health care and an elevated risk for new primary cancers than the general population does.[5] For this reason, there is a growing need for additional specialized health personnel[6] and a need for increased training in survivorship care to support delivery of multidimensional primary care for long-term survivors.[7] For some years now, there has been increasing concern among experts that the services required to meet the physical, social, and emotional needs of cancer survivors will have not been adequately developed.[8]

To adequately develop the strategies and services required to improve the health and care of cancer survivors, reliable data on numbers and time trends are essential. In Switzerland no information was available until recently. The study that we present in the following[9] not only provides data on the number of cancer survivors living in Switzerland today but also delivers information on their characteristics, development over time up to now, and trends in the next 10 years.

Cancer survivors in Switzerland

Data collection by cancer registries for a number of years is sufficient for producing epidemiological data on new cancer diagnoses annually. However, to calculate the number of cancer survivors, cancer registration for a period of 50 years or more is required. Since there is no such data in Switzerland, for our study we used a well-known mathematical model that is based on the connection between incidence, survival, and mortality, estimates missing values using times series, and checks the results by comparison with observed data.

Almost 4 % of the population affected

The results of our study show that the number of cancer survivors has increased sharply since 1990. This group has grown even faster than the rest of the population, and this development has accelerated strongly in recent years. There are about 300,000 persons, or 3.7 % of the population, with a history of cancer living in Switzerland today. This is double the number of cancer survivors of 20 years ago. According to our projection, this number will probably increase by 30 % in the coming 10 years.

Our study also reveals that the group of long-term cancer survivors (20 years or more) shows the greatest increase, rising 140 % (Figure 1). This is testimony to advances in the treatment of cancer. Due to higher general life expectancy in the population and further improvements in treatments, this group is going to grow even larger in the next 10 years. But treatments can cause late toxicities in long-term survivors, such as cardiotoxicity after cytotoxic drugs, cognitive deficits, and osteoporosis. Moreover, persons in this group are at higher risk for other primary cancers, and they frequently report poorer health generally and greater limitations of activities of daily living than persons without a history of cancer.[10,11]

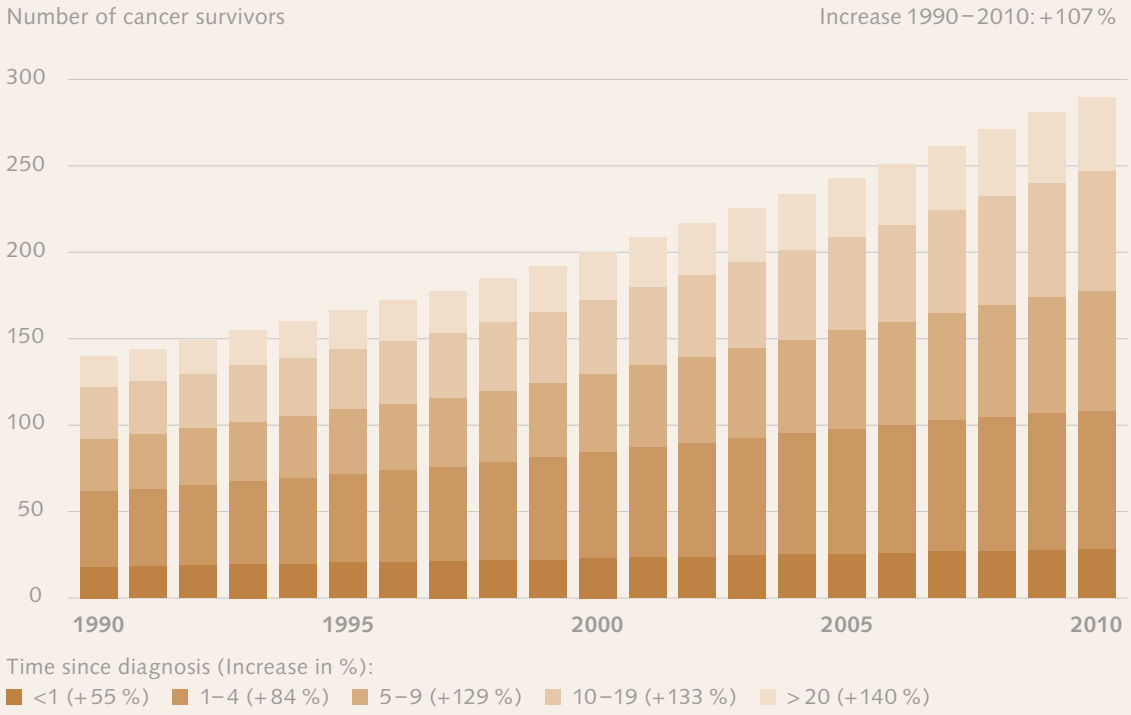
Cancer survivors diagnosed 1 to 5 years ago constitute the largest group, making up 30 % of all cancer survivors. Many of them are still in treatment or are being closely monitored, and most need close management of care by health professionals. In this large, heterogeneous group there are persons with advanced stage cancer, persons who were treated successfully but are suffering side effects of cancer treatments (such as bowel complications after treatment for colorectal tumours, incontinence, and erectile dysfunction after prostatectomy, or lymphoedema after breast cancer treatment), and many persons who are symptom free.

The effects of demography, screening, and treatment

The exponential increase in the number of cancer survivors in Switzerland in the last 20 years is mainly attributable to the increased cancer incidence, increased life expectancy, and growing segment of the aged population.

Types of cancers that can be detected through screening, such as prostate and breast cancer, have contributed greatly to the increase in the incidence rates. The widespread use of prostate specific antigen (PSA) screening has led in Switzerland and worldwide[12] to three- to four-fold increases in incidence

Figure 1
Estimated number of cancer survivors in Switzerland in the period 1990–2010
(all invasive cancer, not including non-melanoma types of skin cancer)



Source: Herrmann C, Cerny T, et al. Cancer survivors in Switzerland: a rapidly growing population to care for. *BMC Cancer.* 2013;13:287.

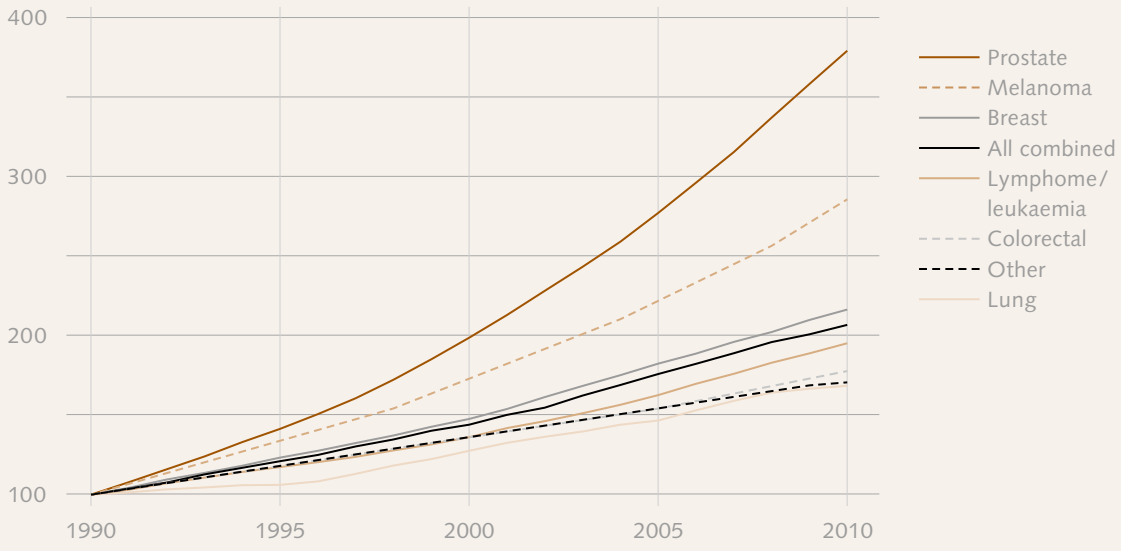
rates for prostate cancer. Moreover, the average age at diagnosis has decreased, which has further contributed to an increase in the survival rate and the prevalence of prostate cancer survivors. The rate for new breast cancer cases has doubled in the last 20 years. However, expert opinions are divided concerning the extent to which early detection and other factors like hormone replacement therapy have contributed to this increase.[13,14]

In the last 20 years there have also been considerable advances in the treatment of many types of cancer. This is especially apparent in the increases in the number of survivors with haematological malignancies and lung cancer by 94 % and 67 %, respectively (Figure 2).

A phenomenon of the Western world

Similar results concerning trend and proportion of the population with a history of cancer have been found in other European countries. In the Nordic countries (Denmark, Finland, Iceland, Norway, and Sweden) 3.4 % to 4.1 % of the population is estimated to be cancer survivors by the end of 2010.[15] In the United Kingdom it is estimated that in 2010 about 3.1 % of the population had a history of cancer,[16] and in Italy the projections for 2010 estimate that 4 % of women and 3 % of men were cancer survivors.[17] Internationally, researchers and stakeholders have only recently begun to focus on this group.[6,18,19] Also in Switzerland, cancer survivors have received insufficient attention up to now.

Figure 2
Trend of prevalence of cancer survivors by type of cancer in Switzerland with highest incidence
expressed as the per cent of the 1990 value.



A challenge for all

Chances of curing cancer are continuing to increase, and patients – including patients with advanced stage cancer – are living longer. In view of our findings, there is an urgent need to inform persons with cancer and health specialists about the long-term effects of cancer and the consequences of treatment as well as to identify psychosocial needs and resources, so as to better contribute towards prevention, maintenance of health, and increased quality of life. Particularly for people below the age of 65, who make up about one-third of cancer survivors, psychological and/or social support and return to work are essential aspects.

To improve the health and care of cancer survivors, new concepts are needed. For one, we need concerted action on the part of everyone involved – researchers, health professionals, patients with cancer, associations and foundations, politicians and the authorities – to deliver optimal care and support to cancer survivors. For another, the relevant scientific data must be collected. The Eastern Switzerland Cancer League, for instance, is conducting a project with the aim to capture needs of cancer survivors that have been insufficiently characterized up to now. In the longer term, the cancer registries and cancer epidemiologists need to include the estimation of the number of cancer survivors and long-term prevalence in the catalogue of regularly published cancer statistics.

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List of completed research projects in 2013

Bordoni Andrea | KFS 2668-08-2010 | CHF 232,700.–
Registro cantonale dei tumori, Istituto cantonale di patologia (ICP), Locarno
Indicators of quality of cancer care in Southern Switzerland

Ess Silvia M. | KFS 2864-08-2011 | CHF 82,500.–
Krebsregister St. Gallen-Appenzell, Krebsliga Ostschweiz, St. Gallen
The burden of metastatic breast cancer in Eastern Switzerland: a population-based study

Martin Brian | KLS 2820-08-2011 | CHF 48,000.–
Arbeitsbereich Bewegung und Gesundheit, Institut für Sozial- und Präventivmedizin, Universität Zürich, Zürich
Impact of physical activity on cancer mortality in Switzerland: results of a 30-year follow-up

Mullis Primus-E. | KLS 2948-02-2012 | CHF 165,000.–
Abteilung für Pädiatrische Endokrinologie, Diabetologie und Stoffwechsel, Universitätsklinik für Kinderheilkunde, Inselspital, Universitätsspital Bern, Bern
Risk of cancer and long-term mortality in children treated with growth hormone: Swiss participation in the EU FP7 project "Safety and Appropriateness of Growth Hormone Treatment in Europe" (SAGhE)

Spörri-Fahrni Adrian | KFS 2763-02-2011 | CHF 261,500.–
Institut für Sozial- und Präventivmedizin (ISPM), Universität Bern, Bern
Privacy preserving probabilistic record linkage (P^3RL) for cancer epidemiology research

Presentation of completed research projects in 2013

Bordoni Andrea | **Indicators of quality of cancer care in Southern Switzerland** (KFS 2668-08-2010)

Assessing the quality of cancer care (QoCC) has become increasingly important to providers, regulators and purchasers of care. As a consequence of yearly renewed international guidelines for cancer treatment, the need to evaluate the real conditions of care in the community appears important. Population-based cancer registry data are therefore essential to describe and reflect real world and routine care as well as to provide regular feedback to healthcare workers and decision makers about the management of a disease in the daily practice and those treatments that are routinely prescribed and/or effective in all patient groups.

Aim of the study

This study aimed to develop evidence-based quality indicators (QIs) for different cancer types (i.e. colorectal, prostate, ovarian and endometrial cancers) to be applied in a population-based setting, with the collaboration of working groups (WG) of local health care providers and an external independent academic advisory board.

Methods

Using the validated Delphi methodology, including literature review of the evidence and integration of local and international expert opinions, a list of QI was defined to assess QoCC. By means of the Ticino Cancer Registry, information on different cancer types was collected.

Results

The QoCC population-based project, involving both public and private hospitals and clinics in the Canton of Ticino, is currently ongoing. So far, a peer-review publication on QI definition has been accepted by BMJ Open, and different newsletters have been produced for the WG, with the aim to define standards of care for each QI in terms of minimum and target requirements. Two publications reporting results on colorectal and prostate cancers are in preparation.

Conclusion and importance for patients

The systematic analysis of QIs allows assessment of immediate changes and improvements in the diagnostic-therapeutic process, which could be translated into a short-term benefit for patients, without waiting for survival analysis that typically needs some years to be produced because of the patients' follow-up. This system of evaluation and auto-evaluation could favour surveillance and monitoring of the comprehensive level of oncological care in Southern Switzerland, clinical performance homogeneity, possible weakness of the clinical network, and finally corrective interventions to be adopted to improve QoCC.

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Ess Silvia M. | **The burden of metastatic breast cancer in Eastern Switzerland: a population-based study** (KFS 2864-08-2011)

Breast cancer is the most frequently diagnosed malignancy among women. Although cancer mortality has been decreasing since 1990, metastatic breast cancer continues to be the most frequent cause of cancer-related death and premature death (before the age 70) among women. Data on the number of affected women, survival among them and factors influencing survival of metastatic breast cancer in Switzerland are scarce.

Objectives

The aim of this study was to quantify the burden of metastatic breast cancer in Eastern Switzerland and to study which patient and tumour characteristics are associated with better survival.

Patients and methods

From the database of the cancer registries of St. Gallen-Appenzell and Grisons-Glarus we identified 7,607 women living in the region with a diagnosis of invasive breast cancer made during or before the start of the study period, which included the years 2003 through 2009. Through chart review and questionnaires filled out by treating physicians we identified women developing metastatic breast cancer after a diagnosis of early breast cancer and women diagnosed with de novo stage IV disease.

Results

We identified 857 patients diagnosed with recurrent systemic or stage IV breast cancer in the years 2003–2009. In 65 % of women metastatic disease developed after 6 months to over 20 years of disease-free survival. These cases had been initially diagnosed with localized (stage I and II) disease (60 %) or locally advanced (stage IIIa-IIIc) disease (40 %). Median age at diagnosis of metastatic disease was 66 years (range 29 to 98 years). Median survival was 24 months. However 15 % (n = 138) lived five years or more. Endocrine sensitivity of the tumour, absence of visceral metastases, age below 70 years, and localized disease were associated with better survival. Differences between rural and urban areas were observed only in patients aged 70 years or older.

Conclusions

The development of new drugs and new strategies in the management of metastatic breast cancer has led to considerable improvement in survival within and outside clinical trials. More research is needed to better understand patient-related factors related to poor survival and factors improving survival and quality of life in this patient group.

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Fotogramm / Tillia, 2013

Martin Brian | **Impact of physical activity on cancer mortality in Switzerland: results of a 30-year follow-up**
(KLS 2820-08-2011)

The World Health Organisation WHO describes physical inactivity as one of the four main risk factors for non-communicable diseases, together with tobacco use, harmful use of alcohol and unhealthy diets. However, there are only very few estimates concerning the potential of physical activity for cancer prevention in Switzerland. Even in the international scientific literature, little can be found about the effects of different domains (domestic, occupational, transport-related and leisure-time) of physical activity behaviour.

Study aim

In a longitudinal study design, the effects of different domains of physical activity behaviour on cancer mortality and on overall mortality in the Swiss population were to be quantified.

Methods

Using an anonymous record linkage procedure, it was possible to connect data from two large cross-sectional health surveys (MONICA and National Research Project 1A), carried out between 1977 and 1993, to mortality data from the Swiss National Cohort. In the 17,663 female (51.1 %) and male study subjects in the age range of 16 to 92 years, 3,878 cases of deaths were observed during up to 32 years of follow-up, including 1,351 cancer deaths.

Results

Individuals with a high leisure-time activity level at baseline (regular vigorous physical activity) had a 31 % reduced risk of dying of cancer in the next decades. Those with a moderate leisure-time activity level (frequent walking or cycling; other frequent activities such as gardening) had a risk reduction of 8 %, although not at a statistically significant level. Regarding all-cause mortality, high and moderate levels of leisure-time activity were associated with statistically significant risk reductions of 27 % and 12 %, respectively, compared to those with low activity levels. There were no protective effects for active transport (walking and cycling) and for work-related physical activities.

Recommendations

The present analyses add evidence of the importance of physical activity, especially during leisure-time, for the prevention of cancer and premature deaths in general also in Switzerland. Improved methodological approaches in future studies may allow better quantification of the potential of active transport and work-related physical activity.

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Mullis Primus-E. | **Risk of cancer and long-term mortality in children treated with growth hormone: Swiss participation in the EU FP7 project "Safety and Appropriateness of Growth Hormone Treatment in Europe" (SAGhE)** (KLS 2948-02-2012)

Growth Hormone (GH) promotes body growth. If GH production is impaired, GH can be substituted with daily injections. A large proportion of patients treated with GH in Switzerland are patients with childhood cancer. However, well-conducted long-term studies on safety of GH replacement therapy are lacking. This project assesses long-term safety after childhood treatment with GH, as a part of the European SAGhE study.

Study aim

The project aims to study long-term efficacy (final height) and quality of life (QoL) in adulthood after GH treatment in childhood and to investigate long-term risk of cancer and mortality.

Methods

We collected medical data from patient files in the hospitals. Information about QoL and current health status was assessed by means of questionnaires. We compared our population to cancer registries and mortality statistics of the Swiss Federal Statistical Office to obtain information about cancer incidence and mortality.

Results

We identified 754 persons treated with GH in Switzerland during childhood who were older than 18 years by 1 March 2011. Of 639 persons contacted, 383 (60 %) returned a questionnaire. QoL depended mainly on the underlying indication for GH treatment. Persons with idiopathic growth hormone deficiency or with associated diseases or syndromes had a QoL comparable to peers. Childhood cancer survivors with GH treatment were at high risk for reduced QoL. It shows that this group needs long-term follow-up. Fourteen patients died and six patients were diagnosed with cancer after GH treatment started. With the low number of cases found in Switzerland, we can only draw conclusions with pooled data from all SAGhE countries. The anonymized data has been delivered to the SAGhE project leader. Publications are expected in 2014.

Potential benefits for patients

The results will aid adaptation of the recommendations for treatment with GH in children to guarantee long-term safety for current and future patients. For former patients, preventive medical check-ups can be planned.

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Spörri-Fahrni Adrian | **Privacy preserving probabilistic record linkage (P^3RL) for cancer epidemiology research** (KFS 2763-02-2011)

Aim of the study

This study aimed to develop a new method for record linkage with securely encrypted person-identifying characteristics, and to test and evaluate the methods using simulated and real cancer registry data.

Methods

Probabilistic record linkage allows the linking of datasets in spite of small differences in the linkage variables, e. g. due to typos or errors in data management. Until recently, it was not possible to link datasets with encrypted variables allowing for minor differences. Small variations made it impossible to combine records that probably belonged to the same person. Privacy preserving probabilistic record linkage methods (P3RL) has person-identifying information, like names, date of birth, or place of residence on Bloom filters. These securely encrypted bit arrays allow calculation of similarities. This facilitates the linkage of datasets even with minor divergences.

Results

In the P3RL project, methods for the secure linkage of person records using Bloom filters were developed, software tools programmed, and the usability as well as the quality of the links tested and evaluated. A first study using simulated data revealed that the quality of the linkage with encrypted versus unencrypted names, date of birth and place of residence was almost identical (precision-recall curve). For a second study with real Swiss cancer data, P3RL methods were applied for the linkage. In previous years, this linkage was feasible with plain person characteristics. In this study, the results of the older record linkage with plain variables served as the gold standard. The linkage using P3RL methods was almost as efficient, and 99.4 % of the former records could be linked with the encrypted linkage variables.

Outlook

Record linkage is a method for combining existing data and is a potentially important source of valuable cancer epidemiological information – for example, information shedding light on the effectiveness of certain cancer screening methods or information for evaluating the long-term effects of cancer treatments. The ability to link cancer-related data sources using important discriminating information such as patient name without breach of confidentiality – privacy preserving probabilistic record linkage (P3RL) – has the potential to transform cancer epidemiology research by making available vast amounts of cancer-related data anonymously and thus heretofore not previously accessible.

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List of approved research projects in 2013

Total funds allocated: CHF 989,700.–

Guessous Idris | KLS 3144-02-2013 | CHF 69,900.–
Département de médecine communautaire, de premier recours et des urgences, Hôpitaux universitaires de Genève (HUG), Genève
Socio-demographic and socio-economic inequalities in cancer screening, Switzerland 1992–2012: trend analyses based on the Swiss Health Survey

Levi Fabio | KFS 3255-08-2013 | CHF 241,000.–
Unité d'épidémiologie du cancer, Institut universitaire de médecine social et préventive Lausanne, Centre hospitalier universitaire vaudois (CHUV), Lausanne
Cancer mortality in Europe: monitoring trends and predictions

Low Nicola | KFS 3264-08-2013 | CHF 233,400.–
Institut für Sozial- und Präventivmedizin (ISPM), Universität Bern, Bern
Human papillomavirus-associated cervical neoplasia in Switzerland at the start of a national vaccination programme: cross-sectional study

Schneider Uwe | KFS 3249-08-2013 | CHF 176,000.–
Forschungsgruppe Medizinische Physik, Universität Zürich und Institut für Radiotherapie, Hirslanden Klinik, Zürich
The impact of image-guided radiotherapy on second cancer incidence

Schoeni-Affolter Franziska | KFS 3165-02-2013 | CHF 125,000.–
Centre de coordination et de données, Etude Suisse de Cohorte VIH, Lausanne
An update of cancer risk in persons infected with HIV in Switzerland

Stöckli Sandro | KLS 3153-02-2013 | CHF 144,400.–
Hals-Nasen-Ohrenklinik, Kantonsspital St. Gallen, St. Gallen
Impact of human papillomavirus (HPV) infection on outcome in surgically treated patients with oropharyngeal squamous cell carcinoma (OPSCC)

Presentation of approved research projects in 2013

Guessous Idris | **Socio-demographic and socio-economic inequalities in cancer screening, Switzerland 1992–2012: trend analyses based on the Swiss Health Survey** (KLS 3144-02-2013)
Duration: 02.09.2013 – 01.09.2014

Cancer morbidity and mortality are associated with socio-demographic and socio-economic status, such as education and income. In Switzerland, cancer screening represents a cost for individuals, depending on their socio-economic status and on their annual health care use. For many years, it has been hypothesized that universal health insurance coverage, high levels of living standards, wealth and well-being in Switzerland would lead to limited inequalities in health and healthcare access.

However, the recent economic downturn in Switzerland has accentuated health access disparities in the general population, as shown by the fact that a substantial proportion of the Swiss adult population is forgoing healthcare for economic reasons. With the delivery of the fifth waves of the Swiss Health Study – a nationally representative cross-sectional survey – we have the possibility to examine cancer screening inequalities in Switzerland and their evolution over the past two decades, from 1992 to 2012.

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Levi Fabio | **Cancer mortality in Europe: monitoring trends and predictions** (KFS 3255-08-2013)
Duration: 01.10.2013 – 30.09.2016

Our aim is to maintain and improve the integrated system of monitoring of cancer mortality in Europe and other areas of the world. Within the project's main aim, in 2013–2016 we plan to exploit cancer mortality data from recent years in order to promptly identify and interpret early signals of evolution, and to further develop and test modelling techniques for interpreting past trends, and for predicting short term trends, which are of key interest for cancer management on a public health scale.

The main expected results include: (1) systematic analysis of cancer mortality in Europe for 2005–2009 and subsequent years when data is available; (2) age-period-cohort analysis of cancer mortality in Europe for the period 1970–2009, i.e. for the cohorts born between 1885 and 1970; (3) annual prediction of cancer mortality in the EU in the current year; (4) systematic analysis of cancer mortality in (Latin) America from 2000 in comparison with Europe; (5) monitoring of the tobacco-related cancer epidemic in Europe, with specific focus on oesophageal and laryngeal cancer; (6) developing methods for evaluating the impact of cancer screening on mortality; (7) analysis of cancer burden and trends in older Europeans; (8) in depth analyses for specific cancer sites, including pleura, skin/melanoma, ovary, testis, prostate, benign prostatic hyperplasia, Hodgkin and non-Hodgkin's lymphomas and sarcomas.

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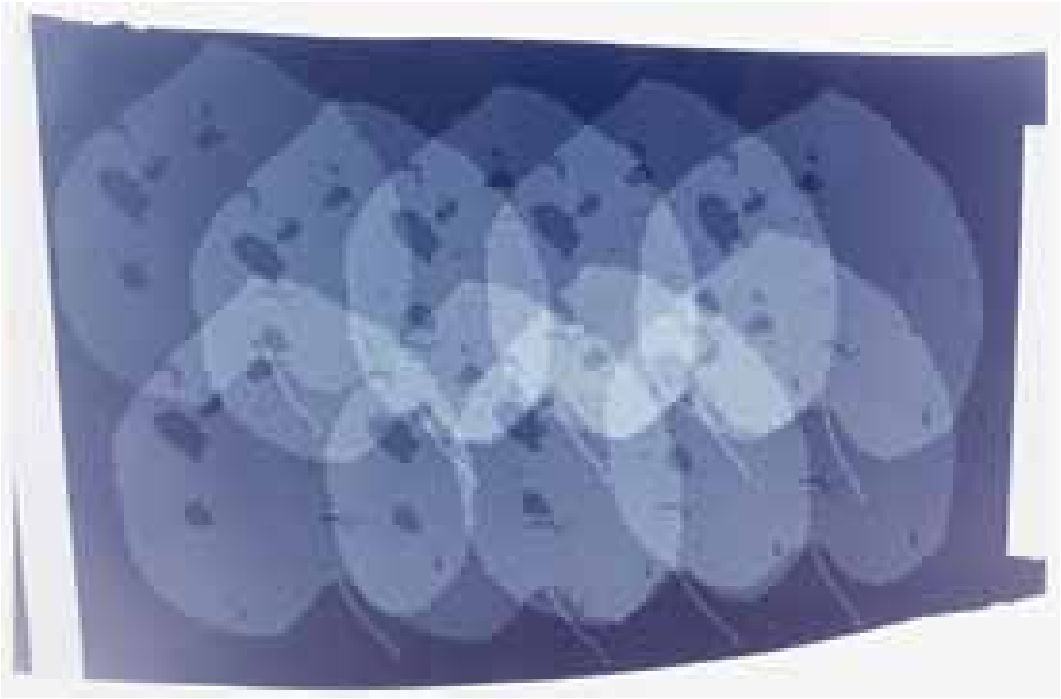
Low Nicola | **Human papillomavirus-associated cervical neoplasia in Switzerland at the start of a national vaccination programme: cross-sectional study** (KFS 3264-08-2013)
Duration: 05.01.2014 – 04.01.2016

Almost all cases of cervical cancer are caused by a viral infection (human papillomavirus, HPV). HPV is transmitted through sexual intercourse; in most cases cancer will appear many years after infection. There are now vaccines that protect against the two most common cancer-causing HPV types (16/18). Since 2008, Switzerland has had cantonal programmes to offer HPV vaccination to girls aged 11–14 years. It is essential to monitor the effectiveness of vaccination in preventing cancer. Trends in pre-cancerous stages can be used to indicate how effective HPV vaccination will be in preventing future cases of cervical cancer.

This project aims to: (1) describe the distribution of HPV types in cervical pre-cancer and cancer before it has been affected by the HPV vaccination programmes, and (2) ex-



Fotogramm / Tillia, 2013

amine factors that might affect the reliability of a system for monitoring outcomes of the vaccination programmes. The project will take place in seven locations in German-, French- and Italian-speaking regions of Switzerland. We will identify women diagnosed with cervical pre-cancer or cancer from laboratory records. We will study biopsy specimens that were used to make the diagnosis and test them for HPV type.

We plan to determine HPV type in 200 specimens from the recent past (2013) and 700 from 2014–2015. We will ask women diagnosed from 2014 onwards for permission to collect additional information about factors that might be associated with cervical pre-cancer and cancer. We will compare basic characteristics of women who do or do not give consent for additional data collection. We will then compare the characteristics of women with cervical pre-cancer and cancer with a random sample of women in the general Swiss population. The benefit of the project is that it will provide the information needed to monitor the future effectiveness and fairness of HPV vaccination in Switzerland.

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Schneider Uwe | **The impact of image-guided radiotherapy on second cancer incidence**
(KFS 3249-08-2013)
Duration: 03.03.2014 – 02.03.2017

Great advances are currently being made in the delivery of external beam radiotherapy with photons through the development of intensity-modulated radiotherapy. These treatment approaches are very precise, both in dose and in the geometrical application of the dose to the patient. For this purpose, such treatment strategies require extensive imaging of the patient, which is usually referred to as image-guided radiotherapy. The additional dose to the patient from such imaging modalities could cause late effects: namely, radiation induced cancer.

It is the aim of this project to perform and analyse dose measurements of therapeutic scatter dose for various treatment techniques and to develop methods for modelling radiation-induced cancer to estimate the magnitude of this effect for the patient. In addition, the gain of modern treatment techniques will be quantified in terms of normal tissue complication and tumour control. The results of the cancer risk estimates and the benefits from the complication and tumour control calculations will be compared for typical clinical treatments. The consequences

based on this analysis will be evaluated in the context of practical considerations regarding the work flow in radiation oncology for clinical patients.

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Schoeni-Affolter Franziska | **An update of cancer risk in persons infected with HIV in Switzerland**
(KFS 3165-02-2013)
Duration: 01.04.2014 – 30.09.2015

SSince the introduction of successful antiretroviral treatment, HIV infection has become a treatable chronic disease. Many HIV-infected patients are now living into their 50s, 60s and beyond. Cancer has become a leading cause of morbidity and mortality in our aging population including HIV-infected persons: some studies indicate a higher risk for HIV-infected persons than for the general population.

With this project we aim at studying this increasing cancer burden in the HIV-positive population in Switzerland. We will examine trends in incidence, survival and mortality of several cancers. General immunodeficiency, lifelong antiretroviral treatment, effects of age and other risk factors will be analysed. Understanding risk factors leading to cancer will allow preventing the worst case through better prevention and targeted screening.

Detailed cancer information from the population-based network of cancer registries will be linked to the anonymized longitudinal clinical data and treatment information of patients in the Swiss HIV Cohort Study (SHCS). This will allow ascertainment of cancer in the SHCS, comparison of cancer incidence to the general Swiss population and analysis of risk factors.

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Stöckli Sandro | **Impact of human papillomavirus (HPV) infection on outcome in surgically treated patients with oropharyngeal squamous cell carcinoma (OPSCC)** (KLS 3153-02-2013)
Duration: 01.01.2013 – 31.12.2014

HPV-related oropharyngeal cancer is associated with significantly improved survival, but it is not clear whether this is due to a better response to chemoradiation or if surgical treatment leads to equivalent results. Therefore, we do not know whether HPV-positive tumours should be treated with radiotherapy or could be treated with less toxic treatment regimens, such as lower radiation dose or abandonment of adjuvant treatment in case of surgical resection.

In this project we will evaluate survival in surgically treated HPV-positive and HPV-negative patients and set up a Swiss data and tissue bank. We will conduct a retrospective chart analysis and investigation of formalin-fixed, paraffin-embedded tissue samples of patients with oropharyngeal cancer treated surgically in Swiss head and neck centres between 2002 and 2010. Futhermore, we will evaluate the impact of different clinical and histological factors and HPV status on outcome in relation to treatment.

HPV-positivity is not integrated in the decision regarding treatment modality. Little is known about the prognostic significance of HPV-positivity in surgically treated patients. Patients with favourable HPV positive OPSCC might benefit from less intensive and less toxic adjuvant treatment after surgery.

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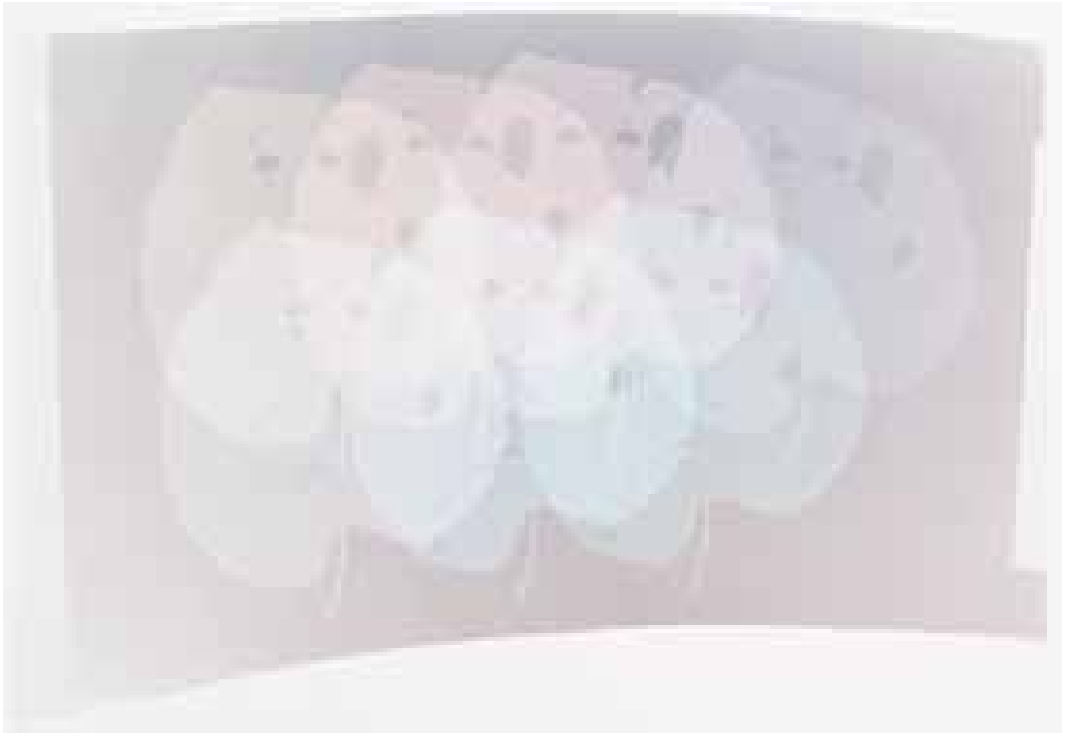

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